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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Erleada

International non-proprietary name: apalutamide

Procedure No. EMEA/H/C/004452/II/0001

Marketing authorisation holder (MAH): Janssen-Cilag International N.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAP	abiraterone acetate plus prednisone
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
BICR	blinded independent central review
CI	Confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration of the United States
GOF	Goodness-of-fit
HR	hazard ratio
HRQoL	health-related quality-of-life
ICH	International Counsel for Harmonization
IHD	ischemic heart disease
IPCW	inverse probability of censoring weighted
ITT	intent-to-treat population
LDH	lactate dehydrogenase
mCSPC	metastatic castration-sensitive prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NM-CRPC	non-metastatic castration-resistant prostate cancer
OS	overall survival
PD	pharmacodynamics
PK	pharmacokinetic
PRO	patient-reported outcome
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SOC	standard-of-care
SPARTAN	ARN-509-003 clinical study
SRE	Skeletal-related events
TEAE	treatment-emergent adverse event
TITAN	56021967PCR3002 clinical study
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 3 June 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) for Erleada based on the results of study 56021927PCR3002 (TITAN study), a randomised, double-blind, placebo-controlled phase 3 study comparing apalutamide plus ADT versus ADT in patients with mHSPC; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to reflect the new indication, to add a warning on ischaemic cardiovascular events and to reflect new safety and efficacy information. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to make editorial update to the SmPC and Labelling. The RMP version 2.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of additional market protection for a new indication. During the procedure the MAH withdrew the application for one additional year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 26 February 2015 (EMA/CHMP/SAWP/553191/2014). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Natalja Karpova

Timetable	Actual dates
Submission date	3 June 2019
Start of procedure:	22 June 2019
CHMP Co-Rapporteur Assessment Report	21 August 2019
CHMP Rapporteur Assessment Report	29 August 2019
PRAC Rapporteur Assessment Report	27 August 2019
PRAC Outcome	5 September 2019
CHMP members comments	13 September 2019
Request for supplementary information (RSI)	19 September 2019
CHMP Rapporteur Assessment Report	21 November 2019
PRAC Rapporteur Assessment Report	25 November 2019
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	28 November 2019
CHMP members comments	02 December 2019
Updated CHMP Rapporteur Assessment Report	06 December 2019
Opinion	12 December 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

This application is to extend the indication of apalutamide to include treatment of metastatic hormono-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT). Hormone-sensitive prostate cancer (mHSPC) is defined as the absence of evidence of castration resistance, defined as prostate cancer that progresses despite castrate levels of testosterone while on treatment with a luteinizing-hormone releasing hormone analogue (LHRHa), or following bilateral orchiectomy (J Clin Oncol. 2008;26:1148–59).

2.1.2. Epidemiology

Prostate cancer is the second most common cancer in men worldwide with an estimated incidence of 1.28 million new cases and approximately 359,000 deaths (GLOBOCAN 2018). It is the most common non-cutaneous related cancer among men in Europe (EU), United States (US), and Latin America/Caribbean comprising approximately 25%, 28%, and 29% of all cancers, respectively (Globocan, 2012). The incidence is less common in Asian regions (WHO SEARO and WPRO) at less than 6%. In the EU and US, prostate cancer is the second leading cause of cancer-related mortality in men.

2.1.3. Clinical presentation and diagnosis

Estimates from European country-specific registries indicate that approximately 15% to 30% of men diagnosed with prostate cancer had metastatic (M1) hormone-sensitive prostate cancer. Metastatic castration-sensitive prostate cancer (mCSPC) may arise as patients previously diagnosed with localized disease go on to develop metastases (M0 at diagnosis), or patients may present with metastases at the time of initial diagnosis (M1 at diagnosis). In either case, mCSPC is an incurable disease.

Treatment aimed at eradicating the primary tumour, typically with surgery or radiation, is unsuccessful in ~30% of men, who develop recurrent disease that usually manifests first as a rise in plasma prostate-specific antigen (PSA) followed by metastasis to distant sites (Stephenson AJ, 2005).

Prognostic factors that influence survival in metastatic castration-sensitive prostate cancer (mCSPC) include high prostate specific antigen (PSA) concentration at diagnosis, high Gleason score, higher primary tumor stage, worse WHO performance status, younger age, and the presence of bone metastases.

2.1.4. Management

As mCSPC is dependent on androgen for growth and survival, depriving prostate cancer cells of androgen is a primary form of therapy for mCSPC patients. ADT has been the basis for the treatment of patients with mHSPC, and results in a median overall survival of 3-4 years. ADT is defined as surgical castration by bilateral orchiectomy or medical castration with gonadotropin-releasing hormone (GnRH) agonists or antagonists (EAU, ESMO, NCCN 2018, Fizazi 2017). The aim of these approaches is to reduce testosterone concentrations. Although the majority of mCSPC patients have an initial response to treatment with ADT, most men progress to castration-resistant prostate cancer within a median of approximately 1 year.

Treatment options for men with mCSPC have expanded beyond ADT alone. Two studies (STAMPEDE ARM C and CHAARTED) provide evidence that combining a short course of docetaxel chemotherapy with ADT in mCSPC resulted in prolonged survival compared with treatment with ADT alone. Docetaxel has recently been approved in combination with ADT, with or without prednisone or prednisolone, for the treatment of patients with metastatic hormone-sensitive prostate cancer (see EPAR docetaxel). Additionally, the STAMPEDE ARM G and LATITUDE studies showed that abiraterone acetate plus low-dose prednisone (AAP) added to ADT was effective in prolonging overall survival (OS) compared with ADT alone. Abiraterone acetate is indicated with prednisone or prednisolone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see EPAR Zytiga). Both ADT plus docetaxel and ADT plus abiraterone/prednisone are recommended by ESMO guideline as first-line treatment of metastatic, hormone-naïve disease (ESMO 2015; ESMO eUpdate 2019).

These therapies are associated with well characterized side effects. Docetaxel is known for myelosuppression, especially febrile neutropenia and neuropathy (see SmPC docetaxel). Abiraterone

acetate has the expected on-target mineralocorticoid side effects such as hypertension, peripheral oedema and hypokalaemia (see SmPC Zytiga).

2.1.5. About the product

Apalutamide (JNJ-56021927, ARN-509) is an orally administered androgen receptor inhibitor that is a selective antagonist of the androgen receptor (AR) without significant agonist properties. Apalutamide antagonizes AR signaling through inhibition of AR nuclear translocation and DNA binding to androgen response elements, a mechanism that is distinct from the first-generation anti-androgens (eg, bicalutamide). Gene transcription of the androgen-responsive genes, prostate-specific antigen, and transmembrane protease serine 2, is inhibited by apalutamide, resulting in concentration-dependent reduction of these protein levels in vitro.

Apalutamide plus ADT is currently approved for the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease.

The MAH applied for the following indication: for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) in adult men (see SmPC section 4.1).

The recommended dose is 240 mg (four 60 mg tablets) as an oral single daily dose. Medical castration with gonadotropin releasing hormone analogue (GnRHa) should be continued during treatment in patients not surgically castrated (see SmPC section 4.2).

2.2. Non-clinical aspects

No new clinical data were submitted in this application (see discussion on non-clinical aspects).

2.2.1. Ecotoxicity/environmental risk assessment

No revised environmental risk assessment (ERA) was submitted as part of this application because the initial ERA presented in the initial MAA was developed to include calculations for Predicted Environmental Concentration and risk characterization ratios that were based on the worst case scenarios assuming that 1% of the population of the EU received apalutamide. Therefore, any additional exposure anticipated resulting from the new indication on mHSPC would already be included in this 1% assumption.

2.2.2. Discussion on non-clinical aspects

No new clinical data have been submitted in this application which was considered acceptable by the CHMP. Regarding the environmental risk assessment, additional exposure anticipated resulting from the new indication on mHSPC would be included in the 1% assumption of the EU population. Based on the current environmental risk assessment, no adverse environmental effects are anticipated as a consequence of the use of apalutamide for the treatment of prostate cancer as indicated in the SmPC.

2.2.3. Conclusion on the non-clinical aspects

The variation to include the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) for Erleada is approvable from the non-clinical point of view. Considering the above data, apalutamide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Clinical studies supporting apalutamide in the mHSPC population

Study Number Phase	Study Design Study Population Primary Objective(s)	Treatment Regimen	Efficacy Endpoint(s)	Number of Subjects / Clinical Cutoff Date
56021927PCR3002 TITAN Phase 3	Randomized (1:1), double-blind, placebo-controlled, multicenter study Men ≥18 years of age with mHSPC To determine if the addition of apalutamide to ADT provides superior efficacy in improving radiographic progression-free survival (rPFS) or overall survival (OS)	Apalutamide 240 mg or placebo once daily; continuous dosing. All subjects who did not undergo surgical castration remain on a stable regimen of ADT.	Dual primary endpoints of rPFS and OS	N=1051[1] 23 November 2018
ARN-509-003 SPARTAN Phase 3	Randomized (2:1), double-blind, placebo-controlled, multicenter study Men ≥18 years of age with high-risk NM-CRPC To demonstrate superiority in the metastasis-free survival (MFS)[2] of men with high-risk NM-CRPC treated with apalutamide versus placebo	Apalutamide 240 mg or Placebo once daily continuous All subjects who did not undergo surgical castration remain on a stable regimen of ADT.	MFS	N=1201[3] 19 September 2017

ADT=androgen deprivation therapy; MFS=metastasis-free survival; mHSPC=metastatic hormone-sensitive prostate cancer; NM-CRPC= non-metastatic castration-resistant prostate cancer; OS=overall survival; rPFS=radiographic progression-free survival

1. In Study 56021927PCR3002, 1052 subjects were randomized, but 1 did not receive treatment, resulting in 1051 subjects in the safety population and 1052 subjects in the intent-to-treat (ITT) population
2. In SPARTAN, MFS is defined as the time from randomization to first evidence of blinded independent central review-confirmed radiographically detectable bone or soft tissue distant metastasis or death due to any cause (whichever occurs earlier) + 1 day.
3. In SPARTAN, 1207 subjects were randomized, but 6 did not receive treatment, resulting in 1207 subjects in the ITT population and 1201 subjects in the safety population.

2.3.2. Pharmacokinetics

Introduction

In support of this application the MAH provided a population PK and exposure-response analysis based on the pivotal Phase 3 study in subjects with mCSPC (Study 3002 [TITAN]), as well as a drug interaction study which evaluated the effects of apalutamide on the PK and pharmacodynamics (PD) of leuprolide (a gonadotropin-releasing hormone analog [GnRHa]) (substudy of Study 3002).

PK Analytical Methods

An assay for the determination of apalutamide (JNJ-56021927 or ARN-509) and N-desmethyl apalutamide (JNJ-56142060) in human plasma was developed and validated for the previous study [Study 003 (SPARTAN)] and was used for the current Study 3002 (TITAN). The PK of apalutamide and N-desmethyl apalutamide following multiple-dose administration of apalutamide in subjects with prostate cancer were thoroughly characterized based on pooled analysis of data from Studies 001, 1010, 1019, and 1020 provided in the original submission (see SmPC section 5.2 and EPAR Erleada).

A bioanalytical method was also developed and validated for measurement of leuprolide in human serum samples.

Population PK analysis

Pooled plots of apalutamide plasma concentrations versus time post the first and latest apalutamide administration in study PCR3002 (TITAN) were examined on linear and semilogarithmic scales (**Figure 1**).

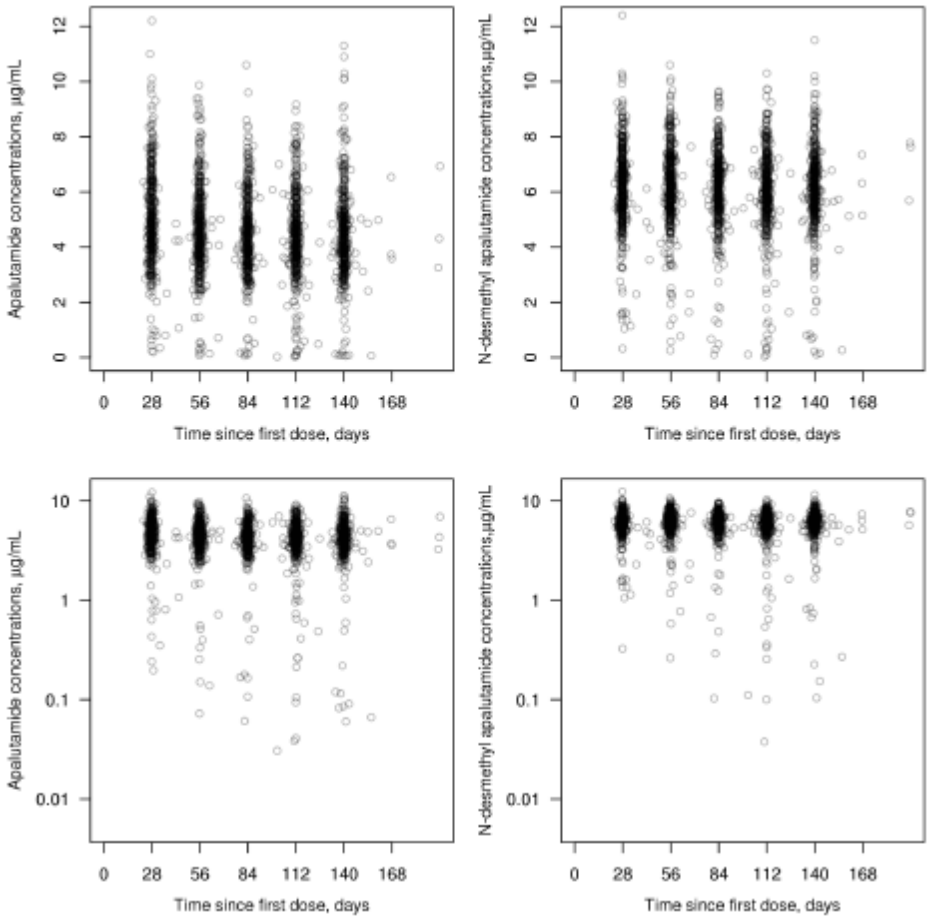


Figure 1: Observed apalutamide (left) and N-desmethyl apalutamide (right) plasma concentrations versus time since first dose on normal scale (upper panels) and logarithmic scale (lower panels)

In total, 2,302 apalutamide and 2,303 N-desmethyl apalutamide plasma concentrations from 501 subjects with evaluable plasma concentration-time data receiving 240 mg apalutamide each day in the apalutamide + ADT arm were used in the population PK analysis. No major differences in these baseline characteristics were observed between patients included in study PCR3002 (TITAN) and the subjects previously included for the development of the population PK model.

A previously developed population PK model was used to characterize the apalutamide and N-desmethyl apalutamide PK and to determine the individual area under the plasma concentration-time curve from time 0 to 24 hours (AUC0-24) at steady state based on the post hoc estimates.

Apalutamide pharmacokinetics were described with an open linear two-compartment disposition model with a time-dependent apparent clearance and apparent first-order absorption, quantified by the absorption rate constant (k_a) after a lag-time (t_{lag}).

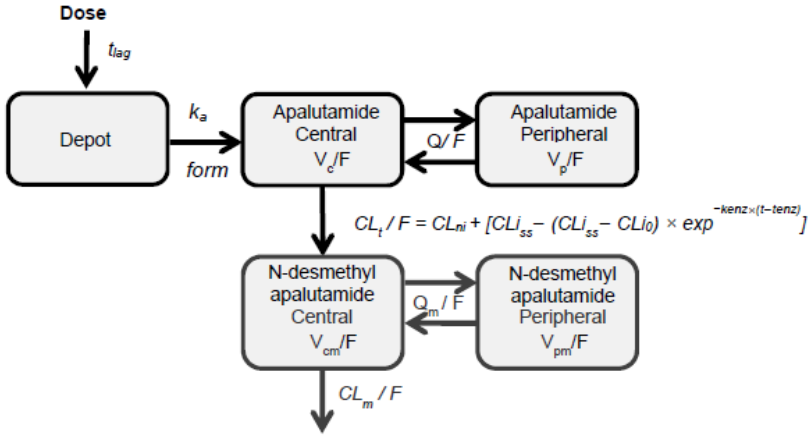
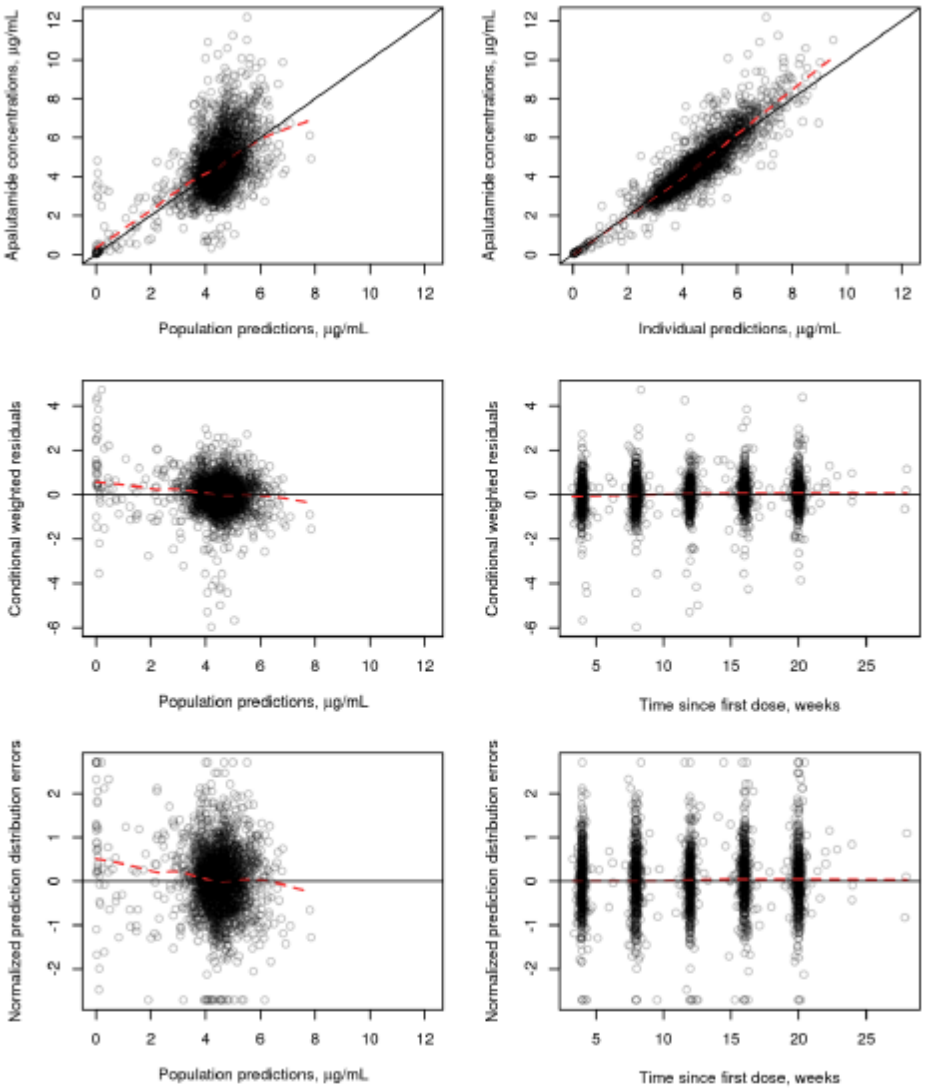


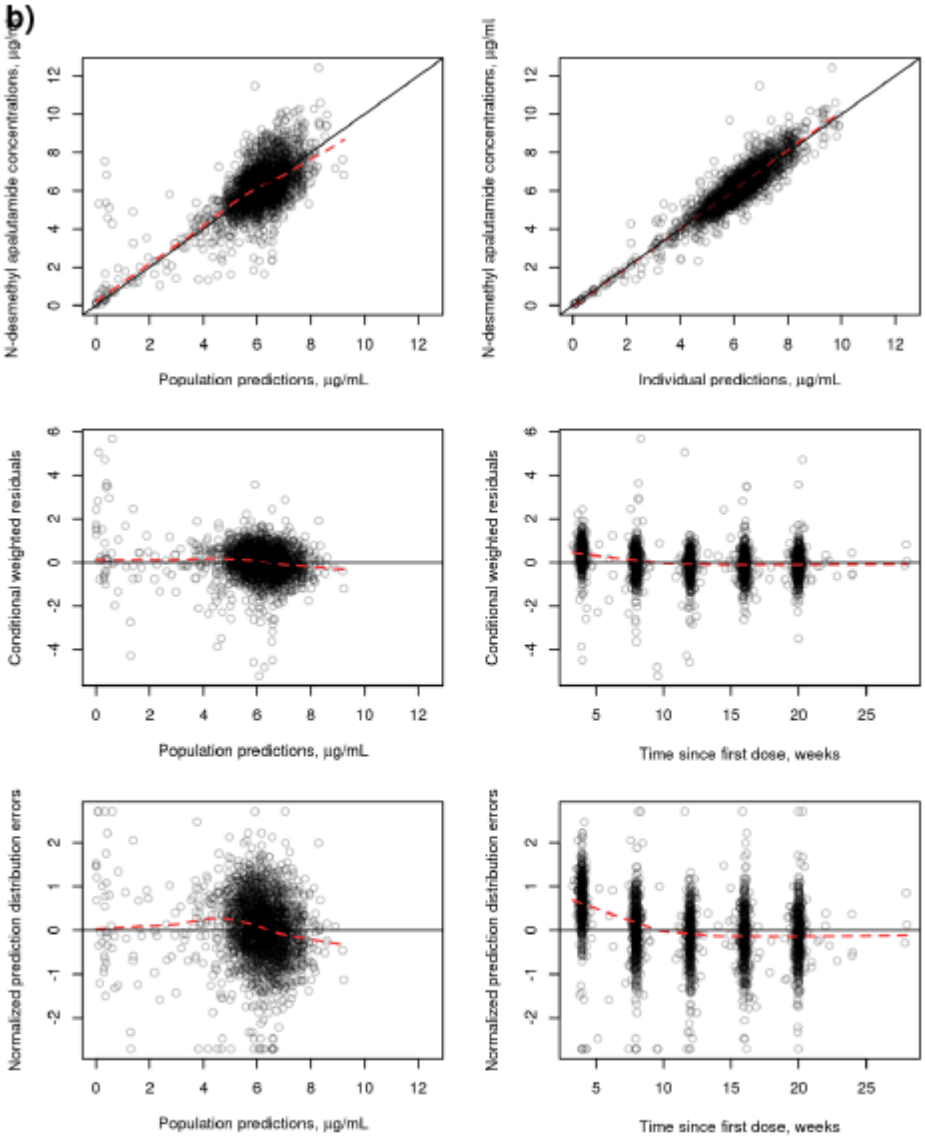
Figure 2: Schematic of the reference population pharmacokinetic model for apalutamide and N-desmethyl apalutamide

The population PK model was parameterized in terms of apparent volumes of distribution of the central (V_c/F) and peripheral (V_p/F) compartments, apparent inter-compartmental clearance (Q/F), and apparent total clearance (C_{Lt}/F). The C_{Lt}/F was composed of a constant, not inducible, clearance (CL_{ni}) and inducible clearance (CL_{i0}) that increased over time until achieving steady-state (CL_{iss}) after the continuous once daily dosing of apalutamide. The inducible clearance was assumed to be concentration independent and the time to achieve steady-state was driven by a first-order turnover rate constant (k_{enz}) after a lag-time needed to initiate the enzyme induction (t_{enz}).

a)

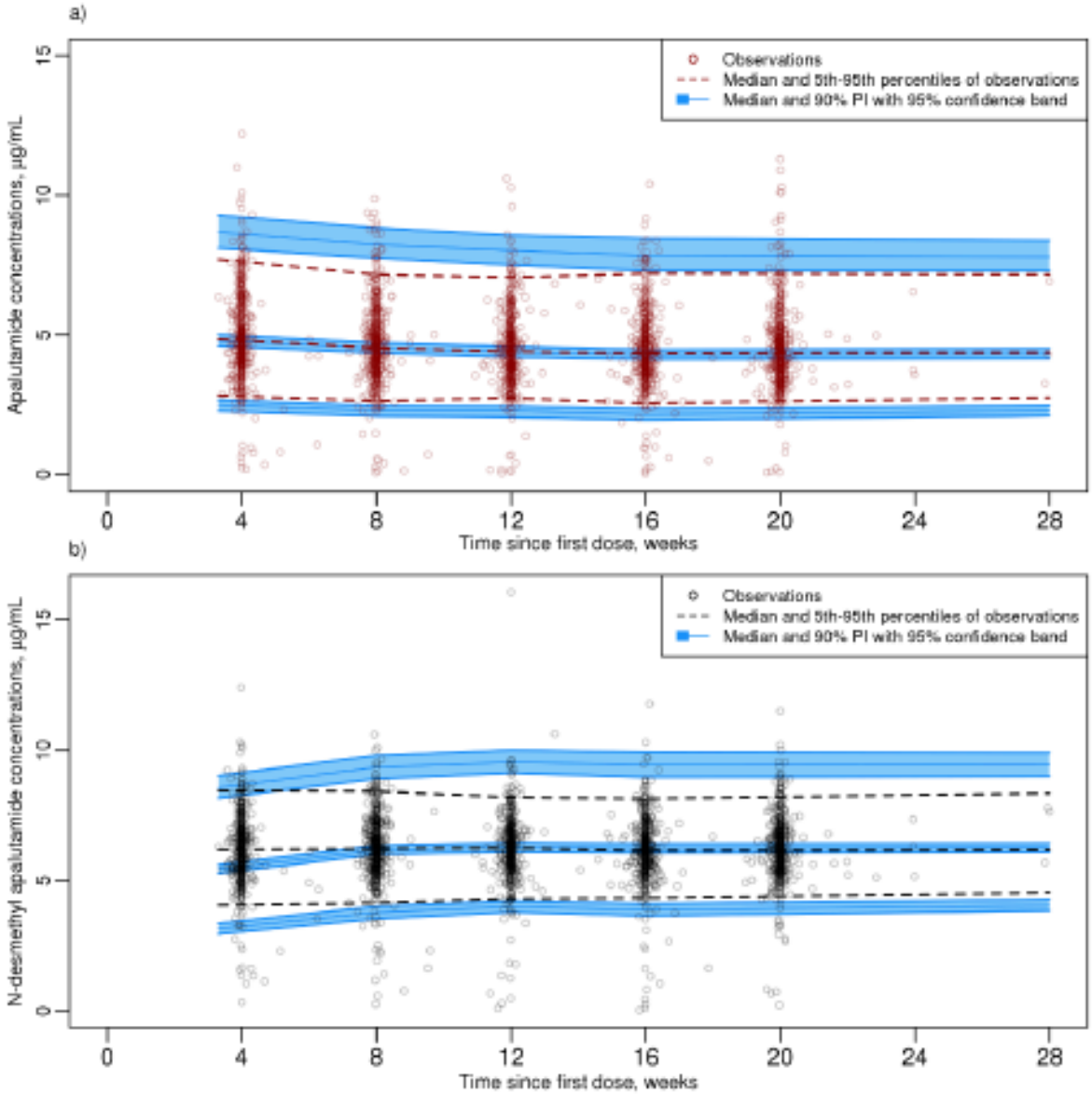


Open circles represent the observations/predictions (upper panels), conditional weighted residuals (middle panels) and the normalized prediction distribution errors (lower panels) for apalutamide; solid black lines represent the identity lines; red dashed lines represent the trend line (lowess, locally weighted scatterplot smoothing).



Open circles represent the observations/predictions (upper panels), conditional weighted residuals (middle panels) and the normalized prediction distribution errors (lower panels) for N-desmethyl apalutamide; solid black lines represent the identity lines; red dashed lines represent the trend line (lowess, locally weighted scatterplot smoothing).

Figure 3: Goodness-of-fit plots for apalutamide (a) and N-desmethyl apalutamide (b) applying the previously developed popPK model for apalutamide to data obtained from subjects randomized in study PCR3002 (TITAN)



The open circles represent the observed concentrations of apalutamide (panel a) and N-desmethyl apalutamide (panel b). The median and 5th and 95th percentiles of the observations are indicated as the dashed line in the same color as the observations. The simulation-derived median and 90% prediction intervals (PI) are accompanied by their 95% confidence intervals and are indicated as blue lines and shaded blue area, respectively.

Figure 4: Visual Predictive Check applying the previously developed model to PCR3002 (TITAN) data for apalutamide (upper panel - a) and N-desmethyl apalutamide (lower panel - b)

The variability in plasma concentrations observed in Study 3002 (TITAN) was slightly lower than the model predicted variability, as evidenced by the visual predictive check provided in **Figure 4**. This external evaluation indicated that the apalutamide PK observed in TITAN was similar to that in subjects included in the dataset used to develop the population PK model. The summary statistics of individual AUC0-24, dose-normalized to 240 mg once daily, were similar to AUC0-24 corrected for the average daily dose for rPFS due to the limited number of dose reductions (7.3% of patients in the apalutamide treatment arm) observed in the TITAN study. Because patients discontinued treatment upon progression

of disease, average daily dose and AUC0-24, corrected for average daily dose, of OS were similar to those of rPFS. In addition, apparent steady-state clearance, apparent steady-state volume, and terminal half-life at steady state of both apalutamide and N-desmethyl apalutamide in the TITAN study were also provided.

Table 2: Summary Statistics for the Individual Exposure Metrics for Apalutamide and N-desmethyl Apalutamide

	Parameter		N [a]	Median	Mean	Minimum	Maximum	CV%
Pharmacokinetic Parameters at Steady State	CL/F (L/h)	Apalutamide	524	2.10	2.14	1.11	7.07	25.8
		N-desmethyl apalutamide		1.57	1.59	0.98	3.74	17.1
	V_{ss}/F (L)	Apalutamide		279	312	85.8	2917	64.5
		N-desmethyl apalutamide		235	240	92.2	588	20.3
	Terminal half-life (days)	Apalutamide		4.21	4.54	1.63	27.5	45.0
		N-desmethyl apalutamide		4.40	4.43	2.03	9.25	1.22
Dose-normalized 240 mg	AUC_{0-24} (µg.h/mL)	Apalutamide	524	115	118	33.9	217	22.0
		Q1	131	91.1	88.6	33.9	101	13.5
		Q2	131	108	108	101	115	3.6
		Q3	131	122	123	115	132	3.9
		Q4	131	149	153	132	217	11.7
		N-desmethyl apalutamide	524	153	155	64.2	245	15.3
		Q1	131	130	126	64.2	140	10.4
		Q2	131	147	147	140	153	2.6
		Q3	131	160	160	153	168	2.8
		Q4	131	180	185	168	245	8.3
Average Daily Dose (rPFS)	Average daily dose (mg)	Apalutamide	502	239	232	78.4	316	9.6
		Placebo	502	239	237	130	445	6.2
	AUC_{0-24} (µg.h/mL)	Apalutamide	502	111	114	28.2	202	23.5
		N-desmethyl apalutamide	502	149	149	53.3	245	17.7

[a] One subject that was randomized but never treated was excluded from this table with exposure summary statistics.
Source: Mod5.3.3.5/PopPKReport/Tab6

Pharmacokinetic interaction studies

Effect of apalutamide on the Pharmacokinetics of Leuprolide

In this application, the drug interaction of apalutamide with leuprolide acetate, a GnRH analogue, was evaluated in a PK substudy of Study 3002 (TITAN).

Table 3: Serum Concentrations of Leuprolide at Baseline and During Treatment Phase After IM or SC Administration of Leuprolide Acetate Alone (Placebo Treatment Group) or in Combination with Apalutamide at 240 mg Once Daily (Apalutamide Treatment Group)

	Leuprolide Acetate + Placebo (Reference)		Leuprolide Acetate + Apalutamide (Test)	
	Pretreatment Baseline (C1D1)	Treatment Phase Average (C3-6)	Pretreatment Baseline (C1D1)	Treatment Phase Average (C3-6)
All Data				
n	17	25	17	31
Mean (CV%)	0.107 (141.0)	0.114 (105.5)	0.309 (152.2)	0.235 (121.9)
Median	0.0601	0.0839	0.153	0.122
Min-max	BQL-0.639	0.0125-0.628	BQL-1.73	0.0125-1.46
Geometric mean	0.0534	0.0820	0.108	0.130
By Administration Route: IM				
n	10	15	6	12
Mean (CV%)	0.126 (148.4)	0.0914 (58.5)	0.394 (166.9)	0.241 (73.6)
Median	0.0668	0.0829	0.165	0.185
Min-max	BQL-0.639	0.0125-0.242	BQL-1.73	0.0616-0.621
Geometric mean	0.0633	0.0767	0.146	0.186
By Administration Route: SC				
n	7	10	11	19
Mean (CV%)	0.0798 (102.3)	0.147 (121.4)	0.262 (137.6)	0.231 (148.2)
Median	0.0261	0.0910	0.0715	0.101
Min-max	BQL-0.199	0.0125-0.628	BQL-1.18	0.0125-1.46
Geometric mean	0.0418	0.0905	0.0916	0.104
By Dose: 22.5 mg				
n	7	15	9	17
Mean (CV%)	0.0819 (96.4)	0.106 (58.2)	0.272 (140.7)	0.296 (119.4)
Median	0.0440	0.0991	0.0782	0.175
Min-max	BQL-0.199	0.0125-0.242	BQL-1.18	0.0125-1.46
Geometric mean	0.0486	0.0872	0.107	0.157
By Administration Route and Dose: 22.5 mg SC				
n	4	6	8	11
Mean (CV%)	0.0625 (145.9)	0.105 (66.3)	0.297 (135.6)	0.299 (141.4)
Median	0.0193	0.0969	0.123	0.122
Min-max	BQL-0.199	0.0125-0.218	BQL-1.18	0.0125-1.46
Geometric mean	0.0300	0.0788	0.111	0.126

Source: Mod5.3.5.1/3002/Attachment/Tab2

2.3.3. Pharmacodynamics

No new pharmacodynamics studies were submitted in support of this application.

2.3.4. PK/PD modelling

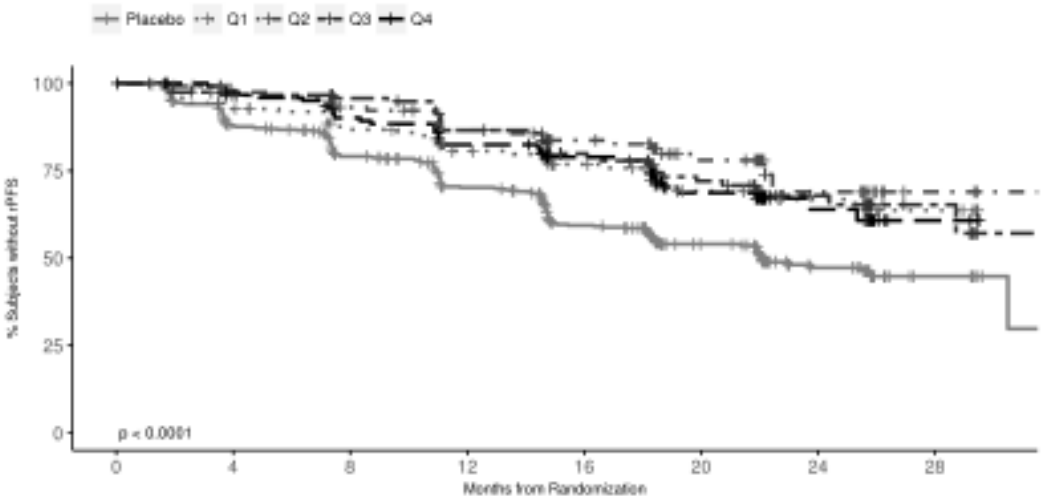
Exposure-efficacy

The exposure-efficacy analysis data contained mesurments from 1,052 patients enrolled in study TITAN, of which 525 received apalutamide+ADT and 527 received placebo+ADT.

The individual AUC0-24 exposure metrics were calculated based on the post hoc estimates using the population PK model and adjusted for the individual average daily dose up to the last day of dosing prior to the event of interest (rPFS or OS) or censoring date. Univariate and multivariate Cox regression models were used to evaluate the relationships between apalutamide exposure and rPFS or OS, adjusted for the stratification factors Gleason score at diagnosis (>7 vs. ≤7), prior docetaxel use (yes vs. no), region (Other Countries vs. North America and European Union) and the prognostic factors, which were statistically significant from the multivariate Cox regression analysis supportive of the primary analysis. The statistically significant prognostic factors for rPFS were the following: Baseline prostate-specific antigen (PSA), Baseline lactate dehydrogenase (LDH), Baseline age, number of bone lesions at Baseline (>10 vs. ≤10), and presence of visceral disease (yes vs. no). The statistically significant prognostic factors for OS were Baseline PSA, Baseline LDH, Baseline ECOG PS (1 vs. 0), number of bone lesions at Baseline (>10 vs. ≤10), and presence of visceral disease (yes vs. no). In addition, type of ADT (surgical castration [ie, bilateral orchiectomy] vs. medical castration [i.e., GnRHa]) was added in the exposure-response analysis of both rPFS and OS.

The observed apalutamide exposure levels following the administration of apalutamide 240 mg once daily with ADT was shown to be efficacious in extending the rPFS (hazard ratio [HR]=0.50; 95% CI: 0.40, 0.62) and OS (HR=0.69; 95% CI: 0.52, 0.92) compared with ADT alone. The univariate Kaplan-Meier analysis showed that within the relatively narrow investigated exposure range, no statistical association could be detected between the dual primary efficacy endpoints (rPFS and OS) and quartiles of apalutamide exposure, expressed as steady-state AUC0-24 for the average daily dose (Figure 5).

A multivariate Cox regression analysis with AUC0-24 as continuous covariate and considering the stratification and prognostic factors mentioned above for both rPFS and OS showed the following results: rPFS stratified HRAUC0-24=0.997 µg.h/mL; 95% CI: 0.990, 1.004 and OS stratified HRAUC0-24=0.994 µg.h/mL; 95% CI: 0.986, 1.003.

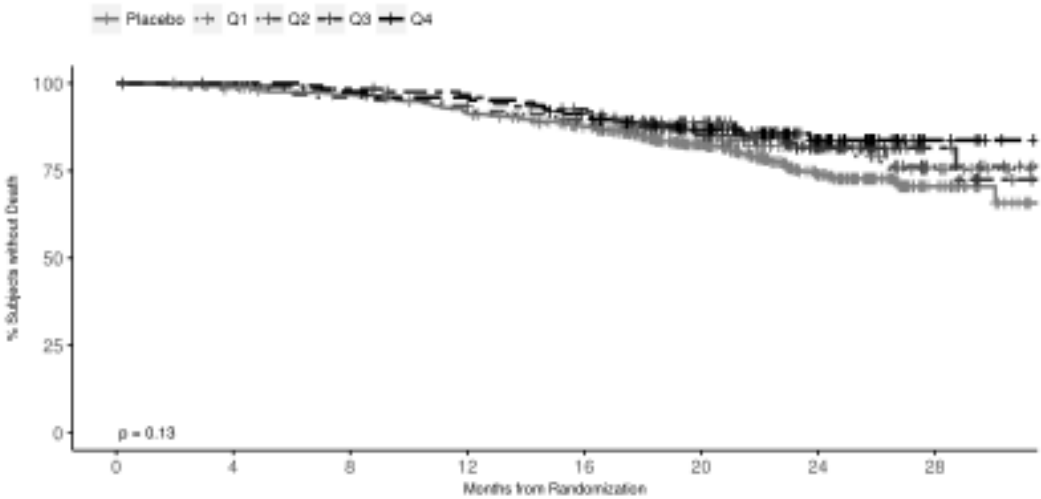


Subjects at risk:

502	422	367	309	225	134	54	11
126	113	101	93	73	38	21	6
125	114	102	91	76	44	14	4
125	111	106	94	79	58	26	8
126	119	107	95	81	44	20	3

0 4 8 12 16 20 24 28
Months from Randomization

Placebo vs Apalutamide Quantiles of Exposure:



Subjects at risk:

501	486	480	451	418	285	137	36
126	122	121	114	107	76	35	12
125	125	120	117	109	82	30	6
125	123	121	117	109	82	50	10
126	126	123	120	111	81	41	8

0 4 8 12 16 20 24 28
Months from Randomization

P-value signifies the difference between exposure-quartiles (Q) of apalutamide and placebo.
Source: Mod5.3.3.5/PopPKReport/FigE2

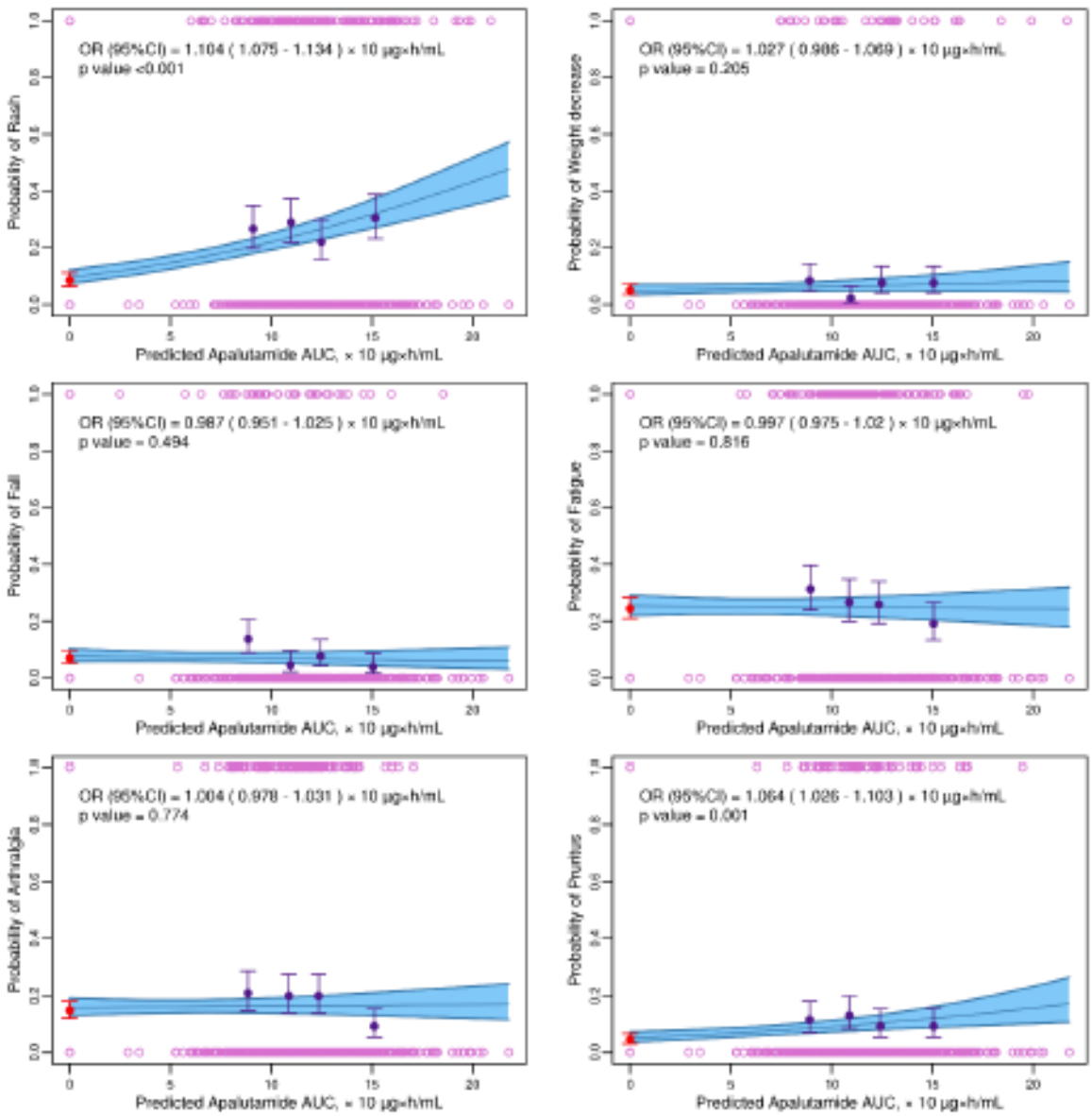
Figure 5: Kaplan-Meier Plot for Radiographic rPFS (Upper Panel) and OS (Lower Panel) as a Function of Placebo and the Apalutamide Steady-state AUC0-24 Quartiles (Q1 to Q4)

Exposure-safety

Data from 1,052 patients (525 apalutamide+ADT and 527 placebo+ADT) enrolled in study TITAN were available for the exposure-safety analysis.

A significantly higher incidence was observed in the apalutamide + ADT treatment arm for skin rash (odds ratio [OR]: 3.98; 95% CI: 2.80, 5.77) and pruritus (OR: 2.51; 95% CI: 1.55, 4.18) compared with the placebo + ADT arm. Comparable incidence rates were observed in the 2 treatment arms for weight decrease, fall, fatigue, and arthralgia. Analogously, the univariate logistic regression showed that skin rash (OR: 1.10 x 10 µg.h/mL; 95% CI: 1.08, 1.13) and pruritus (OR: 1.06 x 10 µg.h/mL; 95% CI: 1.03, 1.10), at any grade, had a statistically significant increase in incidence with increasing apalutamide exposure expressed as predicted steady-state AUC0-24 for the average daily dose (**Figure 6**). On the contrary, weight decrease, fall, fatigue, and arthralgia did not show a statistically significant increase in incidence with increasing apalutamide exposure. When quartiles were examined within the observed exposure range, the incidences of skin rash, pruritus, weight decrease, fall, fatigue, and arthralgia per quartile were similar.

Based on the modeled exposure-TEAE relationships, the incidence of skin rash and pruritus was predicted for typical exposures expected at doses of 240, 180, and 120 mg once daily (**Table 4**). For skin rash, a decrease in exposure following dose reduction is expected to lower the incidence of these TEAEs in the mCSPC population.



The upper and lower open circles represent the presence (y=1) or absence (y=0) of a given treatment-emergent event across the range of the predicted apalutamide AUC_{0-24} exposure respectively. The closed circles depict the observed incidence for the placebo and the quartiles of exposure for the apalutamide arm respectively whereas the corresponding vertical bars represent the exact 95% CI calculated using Wilson's method. Finally, the middle line and its corresponding shaded area represent the model-based exposure-safety relationship and the 95% CI, respectively.
Source: Mod5.3.3.5/PopPKReport/FigE3

Figure 6: Univariate Logistic Regression Representing the Probability of Experiencing Skin Rash, Weight Decrease, Fall, Fatigue, Arthralgia, and Pruritus as Function of Apalutamide AUC_{0-24} at Steady State

Table 4: Model-based Predicted Incidence for the Treatment-emergent Adverse Events Stratified by Apalutamide Dose Level

Model-based Incidence (%) (95% CI) [a]	Simulated Dose Level (Expected Mean Apalutamide AUC_{0-24} at Steady State)		
	120 mg AUC_{0-24} = 60 µg.h/mL	180 mg AUC_{0-24} = 90 µg.h/mL	240 mg AUC_{0-24} = 120 µg.h/mL
Skin rash	16.0 (13.8, 18.5)	20.4 (17.9, 23.2)	25.7 (22.3, 29.4)
Pruritus	7.2 (5.7, 9.0)	8.5 (6.9, 10.5)	10.1 (7.9, 12.8)

[a] Only treatment-emergent adverse events that showed a significant increase with apalutamide exposure were selected for predicting the incidence at other dose levels.

Source: Mod5.3.3.5/PopPKReport/TabE2

2.3.5. Discussion on clinical pharmacology

In support of study number 56021927PCR3002 (also referred to as PCR3002 or TITAN study) three bioanalytical studies for the determination of apalutamide and N-desmethyl apalutamide and leuprolide in human plasma were presented. In general, the pre-study validations of the analytical methods were satisfactory.

In study 3002 (TITAN), a cross-validation for apalutamide and N-desmethyl apalutamide with quality control samples and with study samples from study 3002 (TITAN), was performed and demonstrated that the two methods used have equal performance.

Incurred Samples Re-assay (ISR) was evaluated by additional analyses on a selection of samples plasma for apalutamide and N-desmethyl apalutamide and the other analyte (leuprolide). The results demonstrated reproducibility as of the incurred sample repeats met the acceptance criteria.

The MAH conducted a Phase 3 clinical trial (TITAN) in patients with metastasic hormone sensitive prostate cancer (mHSPC) including 501 patients divided in two arms: placebo+leuprolide and apalutamide+leuoprolide. Several analyses were performed in order to characterize the pharmacokinetics of apalutamide when co-administered with leuprolide and the likely interaction on the pharmacokinetics of leuprolide. Additionally, exposure-efficacy and exposure-safety analyses were conducted to evaluate the effects of apalutamide on the pharmacodynamics of leuprolide.

Higher exposure of leuprolide (42%) was observed in the apalutamide+leuprolide arm versus placebo+leuprolide arm. This was caused by the higher exposure of leuprolide in patients at baseline (pre-treatment with apalutamide). Based on the available data, co-administration with apalutamide had no apparent effect on the steady-state exposure of leuprolide in mHSPC subjects receiving leuprolide acetate (a GnRH analog) (see SmPC section 4.5).

The population PK model previously developed successfully described the observed data from TITAN study. The strategy for external model validation is endorsed. The model slightly over-estimates the inter-individual variability, but standard goodness-of-fit (GOF) and numerical predictive check (NPC) plots concluded the ability of the model to characterize the apalutamide time-course from TITAN study.

No exposure-efficacy relationship was established between apalutamide 240 mg once daily with ADT and OS or rPFS, which suggest that differences in apalutamide exposure given at the proposed schedule are not expected to affect rPFS or OS in patients with mHSPC. The hazard ratio of rPFS (HR=0.5) and OS (HR=0.62) was improved when apalutamide was co-administered with leuprolide compared with ADT alone.

The exposure-safety analysis revealed the relationship between apalutamide exposure and skin rash (OR: 1.10 x 10 µg.h/mL; 95% CI: 1.08, 1.13) and pruritus (OR: 1.06 x 10 µg.h/mL; 95% CI: 1.03, 1.10).

Higher incidence was also observed in the apalutamide+ADT arm versus placebo+ADT arm for skin rash and pruritus. A lack of relationship was demonstrated between apalutamide+leuprolide arm and apalutamide+other ADT agents. Therefore, safety concerns might not be related to the co-administration of apalutamide+leuprolide in patients.

No new pharmacodynamic studies were provided which is considered acceptable. The effect of apalutamide on the QTc interval was thoroughly evaluated in 45 subjects with CRPC in a dedicated QT study (Study 1019) submitted in the original application. Following 240 mg once daily dosing of apalutamide to steady state, the largest change in QT interval corrected with Fridericia's formula (ΔQTcF) was 12.4 msec and the upper bound of its associated 90% CI was 16.0 msec. Across all timepoints the ΔQTcF and upper bounds of their associated 90% CIs were below the threshold of 20 msec for an anticancer agent.

In Study 3002 (TITAN), there were no adverse events associated with ventricular arrhythmias such as QTc prolongation, ventricular tachycardia, or torsade de pointes reported in either treatment arm. Other adverse events which may be associated with QT prolongation were similar between treatments arms; these include syncope and loss of consciousness (combined incidence of both terms was 1.0% in the apalutamide + ADT arm and 0.9% in the placebo + ADT arm), as well as sudden death, sudden cardiac death, cardiorespiratory arrest, and ventricular fibrillation (combined incidence of all 4 terms was 0.6% in the apalutamide + ADT arm and 0.4% in the placebo + ADT arm (see clinical safety) .

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of apalutamide when co-administered with leuprolide in patients with metastatic hormone sensitive prostate cancer has been adequately characterized with pharmacokinetic and pharmacodynamic data from the phase 3 (TITAN) clinical trial. All results from the present combination therapy are in line with the results obtained by the initial application for apalutamide in non-metastatic castration-resistant prostate cancer.

2.4. Clinical efficacy

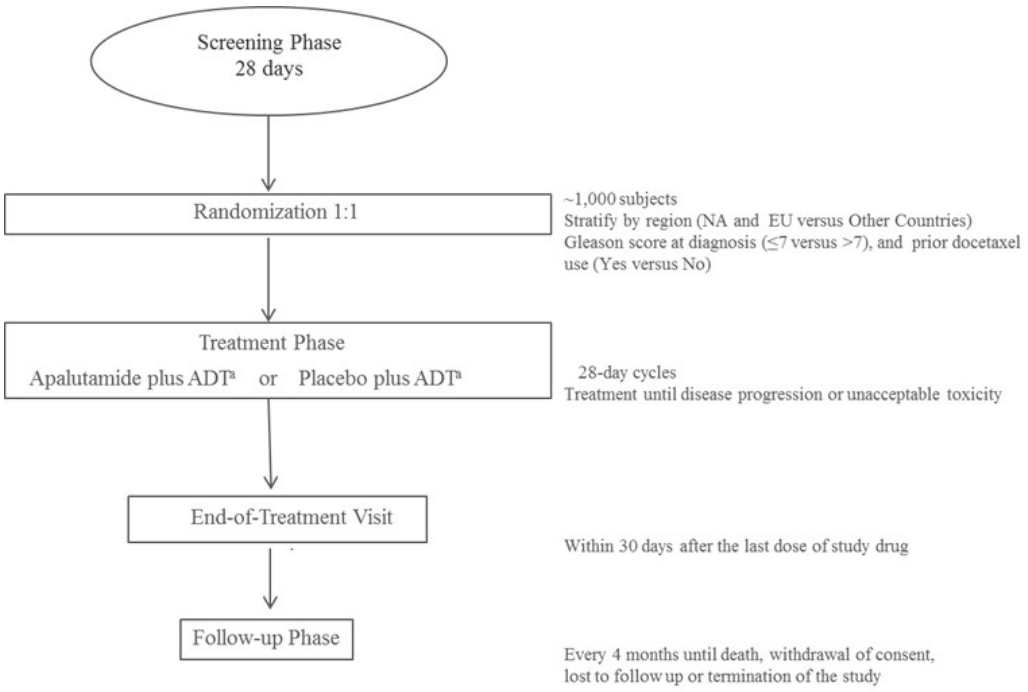
2.4.1. Dose response study

No new dose responses studies were submitted with this application. The posology of apalutamide for the proposed indication (mCSPC) is in line with the currently approved indication (NM-CRPC) which was considered acceptable by the CHMP.

2.4.2. Main study

Study PCR3002 (TITAN)

This is a randomized, double-blind, placebo-controlled, multinational, and multicenter Phase 3 study of apalutamide in patients with mCSPC.



aADT=androgen deprivation therapy, consisting of either medical castration (ie, gonadotropin hormone releasing analog [GnRHa]; agonists or antagonists) or surgical castration (ie, bilateral orchiectomy); EU=European Union; NA=North America

Figure 1. Schematic Overview of the Study

Methods

Study participants

Main Inclusion criteria

- Man ≥18 years of age
- Diagnosis of prostate adenocarcinoma as confirmed by the investigator
- Metastatic disease documented by ≥1 bone lesion(s) on Technetium-99m (99mTc) bone scan. Patients with a single bone lesion must have confirmation of bone metastasis by computed tomography (CT) or magnetic resonance imaging (MRI).
- Androgen deprivation therapy (i.e., medical or surgical castration) must have been started ≥14 days prior to randomization. Patients who start a GnRH agonist ≤28 days prior to randomization will be required to take a first-generation anti-androgen for ≥14 days prior to randomization. The anti-androgen must be discontinued prior to randomization
- ECOG PS grade of 0 or 1
- Patients who received docetaxel treatment must meet the following criteria:
  - Received a maximum of 6 cycles of docetaxel therapy for mCSPC
  - Received the last dose of docetaxel ≤2 months prior to randomization

- Maintained a response to docetaxel of stable disease or better, by investigator assessment of imaging and PSA, prior to randomization

- Other allowed prior treatment for mCSPC: maximum of 1 course of radiation therapy or surgical intervention; radiation therapy for metastatic lesions must be completed prior to randomization; ≤6 months of ADT prior to randomization
- Allowed prior treatments for localized prostate cancer (all treatments must have been completed ≥1 year prior to randomization): ≤3 years total of ADT, all other forms of prior therapies including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies

Main Exclusion criteria

- Known brain metastases
- Lymph nodes as the only sites of metastases
- Visceral (i.e., liver or lung) metastases as the only sites of metastases
- Other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤5 years prior to randomization
- Adequate clinical laboratory values during the Screening Phase
- Prior treatment with other next generation anti-androgens (eg, enzalutamide), CYP17 inhibitors (eg, abiraterone acetate), immunotherapy (eg, sipuleucel-T), radiopharmaceutical agents or other treatments for prostate cancer except those listed in Inclusion Criteria
- Initiation of treatment with a bisphosphonate or denosumab for the management of bone metastasis ≤28 days prior to randomization
- Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate
- Administration of other investigational therapeutic agents, blood product support, growth factor support or invasive surgical procedure (not including surgical castration) ≤28 days prior to randomization or currently enrolled in an investigational study
- Medications known to lower the seizure threshold must be discontinued or substituted ≥28 days prior to randomization.
- Current or prior treatment with anti-epileptic medications for the treatment of seizures. History of seizure or condition that may predispose to seizure (including, but not limited to prior cerebrovascular accident, transient ischemic attack, or loss of consciousness within 1 year prior to randomization; brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect).
- Current evidence of any of the following: a) Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, uncontrolled hypertension, clinically significant arterial or venous thromboembolic events (e.g., pulmonary embolism), or clinically significant ventricular arrhythmias ≤6 months prior to randomization b) Gastrointestinal disorder affecting absorption c) Active infection requiring systemic therapy such as human immunodeficiency virus (HIV) d) Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction
- Subject has known allergies, hypersensitivity, or intolerance to apalutamide or its excipients

Treatments

Patients were randomized in a 1:1 ratio to the apalutamide (240 mg once daily) + ADT arm or matching placebo + ADT arm. Apalutamide, 240 mg daily (4 x 60 mg tablets), or matching placebo (4 tablets) was to be taken orally once daily on a continuous dosing regimen. A cycle of treatment was defined as 28 days. If the subject had radiographic progression without clinical progression and alternate therapy was not initiated, treatment could continue until clinical progression was observed; patients were required to discontinue study drug with documented clinical progression based on protocol-specified criteria.

After discontinuation of study drug, patients had an End-of-Treatment Visit within 30 days after the last dose of study drug.

All patients who did not undergo surgical castration, received and remained on a stable regimen of ADT. The choice of the GnRHa (agonist or antagonist) was at the discretion of the Investigator. Dosing (dose and frequency of administration) was consistent with the prescribing information.

Objectives

The primary objective was to determine if the addition of apalutamide to ADT provides superior efficacy in improving overall survival (OS) or radiographic progression-free survival (rPFS) for patients with mCSPC.

Secondary objectives were to evaluate clinically relevant improvements with addition of apalutamide to ADT including the need for cytotoxic chemotherapy, and delays in pain progression, opioid use for prostate cancer, and skeletal-related events (SREs); to characterize the safety of adding apalutamide to ADT in patients with mCSPC; to characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of apalutamide; to evaluate the concentration of leuprolide and assess the PD effect of leuprolide on testosterone concentrations when used alone or in combination with apalutamide; and to evaluate the treatment effectiveness with the addition of apalutamide to ADT for the subpopulations of patients with low-volume or high-volume mCSPC.

Other Objectives included: to evaluate exploratory biomarkers predictive of response and resistance to treatment; To evaluate patient relevant outcomes including symptoms (ie, pain, fatigue, urination) and function (ie, physical, emotional, social) and health-related quality of life; To evaluate improvements in other clinically relevant endpoints with the addition of apalutamide to ADT.

Outcomes/endpoints

Primary endpoints

The dual-primary endpoints are overall survival (OS) and radiographic progression-free survival (rPFS).

- Overall survival is defined as the time from date of randomization to date of death from any cause.
- Radiographic progression-free survival, as assessed by the investigator is defined as the duration from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first.

Secondary endpoints

- Time to initiation of cytotoxic chemotherapy is defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy.

- Time to pain progression is defined as the time from the date of randomization to the date of the first observation of pain progression. Pain progression is defined as an average increase by 2 points from baseline to >4 in the BPI-SF worst pain intensity (item 3) with no decrease in opioids confirmed ≥3 weeks apart or initiation of chronic opioids, whichever occurs first.
- Time to chronic opioid use is defined as the time from date of randomization to the first date of confirmed chronic opioid use. For patients entering the study without receiving opioids, chronic opioid use is defined as administration of opioid analgesics lasting for ≥3 weeks for oral or ≥7 days for non-oral formulations. For patients entering the study already receiving opioids, chronic opioid use is defined as a ≥30% increase in total daily dose of the opioid analgesics lasting for ≥3 weeks for oral or ≥7 days for non-oral formulations.
- Time to Skeletal-related event (SRE) is defined as the time from the date of randomization to the date of the first observation of an SRE. An SRE is defined as the occurrence of either a pathological fracture, or spinal cord compression, or radiation to bone, or surgery to bone.

Other Endpoints

- Time to symptomatic local progression such as urethral obstruction or bladder outlet obstruction, is defined as the time from date of randomization to date of symptomatic local progression, whichever occurs first
- Time to PSA progression is defined as the time from the date of randomization to the date of PSA progression based on PCWG2 criteria
- Explore response markers for apalutamide, AR gene anomalies and other markers previously shown to be responsible for resistance to apalutamide
- Prostate cancer-specific survival is defined as the time from randomization to the date of death if attributed to prostate cancer
- PFS2 is defined as the time from date of randomization to date of first occurrence of disease progression on first subsequent therapy for prostate cancer or death, whichever occurs first
- Time to ECOG PS grade deterioration is defined as the time from date of randomization to the first date of deterioration in ECOG PS grade (defined as the worsening of ECOG PS grade by at least 1 point)
- Change from baseline over time in each of the subscales of FACT-P, EQ-5D-5L VAS, BPI-SF interference subscale and BFI:

  PRO data for the BPI-SF and BFI were collected for seven days at baseline and every cycle through the end of treatment. The FACT-P and EQ-5D-5L were completed for one day (the last day of the 7 days the BPI-SF and BFI were collected) every cycle from baseline to Cycle 7, and then every 2 months thereafter until end of treatment. All PROs were collected, in the same way, during the Follow-up Phase at Months 4, 8 and 12.

Sample size

An overall type I error of 5% was planned for this study. This study utilizes the dual-primary endpoints of rPFS and OS with a 0.005 level of significance allocated for the rPFS endpoint and 0.045 allocated for OS. The study was considered a success if at least one of the dual-primary endpoints was statistically significant.

It was assumed that the failure distribution of the dual-primary endpoint, rPFS, follows an exponential distribution with a constant hazard rate. It was estimated that approximately 368 rPFS events would be required to provide at least 85% power in detecting an HR of 0.67 (median rPFS of 20 months for the control group [ADT] versus 30 months for the treatment group of apalutamide plus ADT) at a 2-tailed significance level of 0.005. The assumption of 20 months for the control group was an estimate based on published data (Gravis 2013, James 2016, Sweeney 2015). The study would also provide sufficient power (approximately 80%) to detect an HR of 0.75 in the dual-primary endpoint of OS based on an assumed OS median of 44 months (Gravis 2013, Sweeney 2015) for the control group (ADT) (i.e., 44 months versus 59 months). Approximately 410 death events were required for the final analysis to detect the assumed HR at a 2-tailed significance level of 0.045 with an enrollment duration of approximately 30 months (approximately 1,000 patients). The total study duration was estimated to be approximately 54 months to obtain 410 deaths.

Randomisation

Patients were randomized in a 1:1 ratio to receive apalutamide plus ADT or placebo plus ADT. Patients were stratified by Gleason score at diagnosis (≤7 versus >7), region (North America [NA] and European Union [EU] versus Other Countries), and prior docetaxel use (Yes versus No). The randomization was balanced by using randomly permuted blocks. The interactive web response system (IWRS) assigned a unique treatment code, which dictated the treatment assignment and matching study drug kit for each subject.

Blinding (masking)

The study was double-blind.

All patients and study team members associated with the study conduct were to remain blinded to treatment group assignment until the study is unblinded. Unblinding was allowed in the case of a safety or a medical emergency, or for conducting data review by the IDMC as outlined in the IDMC Charter. Unblinding was also possible after the subject discontinues from the Treatment Phase of study because of radiographic progression and the investigator felt this information is essential to determine the next course of therapy. Unblinding a subject for this situation was only possible after discussion with the sponsor's medical officer. Patients who have had their treatment assignment unblinded were discontinued from the Treatment Phase and entered in the Follow-up Phase.

Statistical methods

The ITT population includes all randomized patients and are classified according to their assigned treatment group, regardless of the actual treatment received. Subject disposition and efficacy analyses are performed on data from the ITT population.

The safety population includes all patients who received at least 1 dose of study drug. The PRO population includes randomized subjects who have completed at least the baseline assessment of BPI-SF, BFI, FACT-P or EQ-5D-5L questionnaires.

Kaplan-Meier product limit method and Cox proportional hazards model were used to estimate the time-to-event variables and to obtain the hazard ratio (HR) along with the associated confidence intervals (CIs). Unless otherwise specified, stratified log-rank test was used to test the treatment effect for time-to-event variables. A subject without an event at the time of analysis was censored at the last known date the subject did not have an event. Subgroup analysis was performed based on data from patients

with low volume and those with high volume mCSPC. High volume mCSPC is defined as 1) visceral metastases and at least 1 bone lesion or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low volume mCSPC is defined as the presence of bone lesion(s) not meeting the definition of high volume mCSPC.

The dual-primary efficacy endpoints for the TITAN study were rPFS and OS. In general, a two-sided significance level of $\alpha = 0.05$ was used for all hypothesis testing and all CIs were calculated using the two-sided 95% confidence level, unless otherwise specified. For rPFS and OS the testing used the Fallback Method (Wiens 2005). The rPFS endpoint was tested first at the two-sided 0.005 level of significance. If rPFS was not statistically significant, the OS endpoint was to be tested at the two-sided 0.045 level of significance; if rPFS was statistically significant, the OS endpoint was to be tested at the two-sided 0.05 level of significance.

Radiographic progressive disease

Radiographic progressive disease is defined as one of the following:

1. Progression of soft tissue lesions measured by CT or MRI as defined by modified RECIST 1.1.
2. A patient was considered to have radiographic progression by bone scan if:
   - Patients who were observed to have ≥2 new bone lesions on the Cycle 3 bone scan compared with the baseline bone scan had a confirmatory bone scan performed at ≥6 weeks later and their scans were subjected to the 2+2 rule as follows: Patients with a confirmatory scan that showed ≥2 new bone lesions compared with the Cycle 3 bone scan (ie, at least 4 new lesions compared with the baseline bone scan) were considered to have radiographic progression by bone scan. The date of progression was the date of the Cycle 3 bone scan; Patients whose confirmatory scan did not show ≥2 new bone lesions compared with the Cycle 3 bone scan were not considered to have radiographic progression by bone scan. In order to be considered to have radiographic progression by bone scan, these patients had to have a subsequent bone scan with observation of ≥2 new bone lesions compared with the Cycle 3 bone scan. The date of progression would be the date of the first subsequent bone scan with ≥2 new bone lesions compared with the Cycle 3 bone scan.
   - Patients whose Cycle 3 bone scan did not show ≥2 new bone lesions compared with baseline bone scan did not have a confirmatory bone scan performed and were not considered to have radiographic progression by bone scan at that time. In order to be considered to have radiographic progression by bone scan, these patients had to have a subsequent bone scan with ≥2 new bone lesions compared with the baseline bone scan.

Radiographic progression-free survival data for patients with no evidence of radiographic progressive disease was censored on the date of the last tumour assessment (or, if no tumour assessment was performed after the baseline visit, at the date of randomization).

Scenario	Censoring rule
No tumor assessment at Baseline or No tumor assessment after Baseline	Censored on the date of randomization
Subjects who are lost to follow-up or withdraw from study	Censored on the date of the last tumor assessment
Subjects who receive selected new systemic anti-cancer therapy prior to documented disease progression or death	Censored on the date of the last tumor assessment prior to the start of the new systemic anti-cancer therapy or death
Subjects with no evidence of radiographic progressive disease or death	Censored on the date of the last tumor assessment
Subjects with 2 or more consecutive missing assessments followed by evidence of radiographic progressive disease or death	Censored on the date of the last tumor assessment before the missing assessments.

The progression of soft tissue lesions was measured by CT or MRI as defined by modified RECIST 1.1.

The primary analysis compared the rPFS distributions in the 2 treatment groups using a two-sided log-rank test, stratified by Gleason score at diagnosis (≤7 vs. >7), region (NA, EU, vs. other countries), and prior docetaxel use (Yes vs. No) at the 0.005 significance level. At the time of primary analysis of rPFS it was projected that approximately 50% of the total number of required events for the OS analysis would be observed. Stratified Cox proportional-hazard model was used to obtain the HR and its 95% CI. Non-stratified log rank test was performed as a sensitivity analysis.

To assess the consistency of treatment benefit with respect to the primary efficacy endpoint of rPFS across important subgroups. The comparison between the two treatment groups was evaluated using the hazard ratio with its 95% CI from a univariate Cox regression model in each subgroup.

Multivariate Cox regression analysis, adjusting for important selected prognostic factors, were performed as supportive analysis, as appropriate. The adjusted hazard ratio and its 95% CI for treatment and each factor are provided. The following baseline covariates were considered for inclusion in the model: PSA, lactate dehydrogenase (LDH), alkaline phosphatase, hemoglobin, pain at baseline, age, ECOG PS grade (0 vs. 1), number of bone lesions at baseline (≤10 vs. >10), presence of visceral disease (yes vs. no), receipt of localized therapy (yes vs. no), geographic region (NA/EU vs. other countries), gleason score (≤7 vs. >7) and prior docetaxel use (yes vs. no).

Note: To evaluate the lack of bias in the investigator's assessment of rPFS, an audit plan was implemented. The primary audit plan utilizes the method proposed by Dodd (NCI method). The audit plan was implemented as a supportive plan. All scans were collected in a central location for blinded independent review. Stratified simple random sampling was used to make sure the sample was truly representative of the entire population. Six-hundred (~60%) patients were randomly selected for the blinded independent central review (BICR) review before unblinding, stratified by the same factors used for stratified randomization: Gleason score at diagnosis, prior docetaxel use, and geographic region.

<u>Overall survival</u>

For the dual-primary OS endpoint, 2 interim analyses are planned for this study after observing approximately 50% (~205 events) and approximately 70% (~287 events) of the total number of required (410) events. At the time of the first interim analysis of OS, the final analysis of the rPFS dual-primary endpoint will also be performed. The primary analysis for the comparison of the OS distributions between the two treatment groups was carried out using the stratified log rank test at a two-sided overall significance level of 0.05 after rPFS achieved the statistical significance at 0.005 level. A pre-specified Wang-Tsiatis power boundaries characterized by a shape parameter of 0.2 was used for the interim analysis of OS. The analysis methods for OS were similar to those for rPFS. In addition, 6-month, 12-month, 24-month, and 36-month survival rates were estimated using the Kaplan-Meier method. Subgroup analyses on patients with low or high volume mCSPC disease were performed without alpha spending assigned without adjustment for multiplicity. Sensitivity analyses could also be conducted.

The general hypothesis used to address the primary objective was as follows:

H0: The survival distributions (rPFS or OS) of the experimental group (apalutamide + ADT) SE(t), and that of the control group (placebo + ADT), SC(t), are equal:

$$SE(t) = SC(t), \text{ for all } t > 0$$

H1: The survival distributions (rPFS or OS) are not equal:

$$SE(t) \neq S(t), \text{ for some } t > 0$$

Analysis of secondary endpoints

The statistical testing of the secondary endpoints was performed by at the time of the first interim analysis using fixed sequence testing according to the following pre-specified order considering clinical importance and data maturity: time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to SRE. This procedure controls the overall level of significance at the 2-tailed, with α set at 0.05.

Results

Participant flow

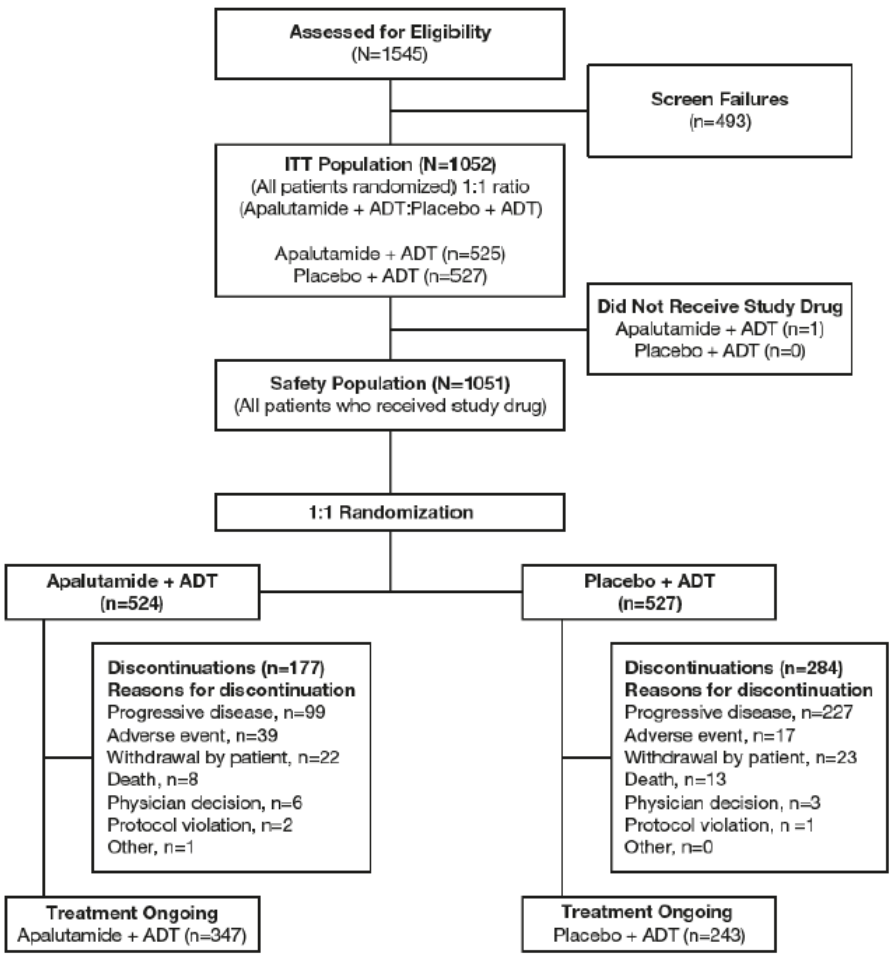


Figure 7: Patient Disposition Flowchart

Recruitment

Enrolment of approximately 1,000 patients was planned for this study. From 1545 patients assessed for eligibility a total of 1052 patients were randomly assigned to treatment (525 patients to the apalutamide + ADT arm and 527 patients to the placebo + ADT arm) and comprise the ITT (intent-to treat) population. One subject was assigned to the apalutamide + ADT arm but withdrew consent prior to treatment, resulting in 1051 patients in the safety population. The first subject signed informed consent on 9 December 2015 and the last subject signed informed consent on 29 June 2017.

Twenty-three countries and 260 sites participated in the study. The clinical cut-off (CCO) date for this report was 23 November 2018.

Conduct of the study

Protocol amendments

There were 4 amendments to the original protocol, dated 24 June 2015. Major changes to the conduct of the study are described in the following table.

Table 1. Summary of Protocol Amendments for PCR3002

Amendment 1 8 April 2016 Substantial	• Inclusion criteria were amended based on feedback from investigators or steering committee members: – inclusion criterion 2 added subjects with high-volume metastatic castration-sensitive prostate cancer (mCSPC) and removed the requirement for histologic evidence of prostate adenocarcinoma from a metastatic lesion for subjects who had been diagnosed more than 5 years prior to randomization – inclusion criterion 3 was changed to allow a single bone lesion on bone scan, – inclusion criterion 4 restricted Eastern Cooperative Oncology Group (ECOG) performance status to grade 0 or 1 (removed eligibility for grade 2), – exclusion criterion 8 clarified that bisphosphonates and denosumab for the management of bone metastasis are not allowed, – exclusion criterion 10 incorporated blood product and growth factor support. • Criteria for prior prostate cancer therapy were modified based on Steering Committee feedback. • Collection of trough pharmacokinetic samples became mandatory, clarified collection (voluntary) and volume (4 mL) of PK samples for leuprolide study, and removed collection of circulating tumor cells. • Local amendments to Japan and the Czech Republic were incorporated
Amendment 2 2 February 2017 Substantial	• PK sub-study for leuprolide amended to allow leuprolide doses of 11.25 mg, 22.5 mg, 30 mg, and 45 mg administered by subcutaneous or intramuscular route. • Description of analysis of dual primary endpoints revised to clarify that subgroup analysis by volume of disease will be performed for both endpoints (rPFS and OS). • Clarification that timing for the interim analysis of OS and final analysis of rPFS may not be in alignment if the number of death events for the interim analysis of OS would require an extended delay in the analysis of the rPFS endpoint

Amendment 3 22 February 2018 Substantial	• Open-label Extension Phase revised to include information and details for the crossover to open-label apalutamide after study unblinding, such as details on the Cross-over Eligibility Phase, timing of patient-reported outcomes and biomarker collection, information on collection of additional endpoints, timing of serum chemistry and hematology sampling. • Interim analysis was revised to occur at approximately 60% of events (previously 50%), due to external data relating to study population.
Amendment 4 5 September 2018	• The 2 interim analyses planned for this study were changed to observing approximately 50% (previously 60%) and 70% (previously 75%) of the total number of required (410) OS events, based on lower number of OS events and on recent data from a Phase 3 apalutamide clinical study. • Updates were made to restricted concomitant medications based on the latest available information on the potential for drug interactions with apalutamide.

Protocol deviations

Protocol deviations were recorded for 9.3% of patients overall, and were mostly deviations from entry criteria. Slightly more patients in the apalutamide + ADT arm (6.5%) did not satisfy all entry criteria compared with the placebo + ADT arm (4.2%). The most common eligibility violations in both treatment arms were due to ADT not started within the required time frame (15 patients total, 1.4%) or prior therapies for localized prostate cancer not stopped in time per protocol (9 patients total, 0.9%). Deviations in the "Other" category included patients whose treatment was unblinded without Sponsor consultation, or patients missing efficacy assessments.

Three patients had their study treatment discontinued due to protocol deviations. The remaining deviations were considered by the sponsor unlikely to influence the interpretation of study results or pose a safety risk to the patients.

Table 5: Patients with Major Protocol Deviations; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide	Total
Analysis Set: Intent-to-treat population	527	525	1052
Subjects with major protocol deviations	45 (8.5%)	53 (10.1%)	98 (9.3%)
Entered but did not satisfy criteria	22 (4.2%)	34 (6.5%)	56 (5.3%)
Received a disallowed concomitant treatment	13 (2.5%)	11 (2.1%)	24 (2.3%)
Developed withdrawal criteria but not withdrawn	5 (0.9%)	4 (0.8%)	9 (0.9%)
Other	5 (0.9%)	4 (0.8%)	9 (0.9%)
Received wrong treatment or incorrect dose	1 (0.2%)	1 (0.2%)	2 (0.2%)

Note: For each deviation, subjects are included only once, even if they experienced multiple events in that deviation. Subjects may appear in more than one category.

Table 6: Patients with Major Protocol Deviations for Eligibility Criteria Not Met; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide	Total
Analysis set: Intent-to-treat population	527	525	1052
Subjects with major protocol deviations for inclusion criteria not met	16 (3.0%)	22 (4.2%)	38 (3.6%)
IN05 - ADT started within necessary timelines prior to randomization	7 (1.3%)	8 (1.5%)	15 (1.4%)
IN11 - Prior therapies for localized prostate cancer discontinued in time.	5 (0.9%)	4 (0.8%)	9 (0.9%)
IN06 - Meet requirements for response to prior docetaxal therapy	2 (0.4%)	5 (1.0%)	7 (0.7%)
IN10 - One course of radiation or surgical intervention completed prior to randomization	1 (0.2%)	4 (0.8%)	5 (0.5%)
IN02 - Prostate Cancer diagnosis confirmed	0	1 (0.2%)	1 (0.1%)
IN03 - Metastatic disease documented	0	1 (0.2%)	1 (0.1%)
IN09 - ICF Signed	1 (0.2%)	0	1 (0.1%)
Subjects with major protocol deviations for exclusion criteria not met	6 (1.1%)	10 (1.9%)	16 (1.5%)
EX08 - Treatment with bisphosphonate or denosumab for bone metastasis <=28 days prior to randomization	4 (0.8%)	3 (0.6%)	7 (0.7%)
EX09 - Does not meet washout criteria for prohibited medications	0	3 (0.6%)	3 (0.3%)
EX10 - Administration of investigational agent, supportive care or surgical procedures <=28 days before randomization	1 (0.2%)	2 (0.4%)	3 (0.3%)
EX12 - Other medical condition that may confound assessment	1 (0.2%)	2 (0.4%)	3 (0.3%)
EX01 - Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate	0	1 (0.2%)	1 (0.1%)
EX11 - Anti-epileptic medications, history of predisposition to seizure	0	1 (0.2%)	1 (0.1%)
EX14 - Any condition or situation that in the opinion of the investigator, would preclude participation in this study	0	1 (0.2%)	1 (0.1%)

Note: For each deviation, subjects are included only once, even if they experienced multiple events in that deviation. Subjects may appear in more than one category.

Baseline data

Table 7: Demographics; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide	Total
Analysis set: Intent-to-treat population	527	525	1052
Age, years			
N	527	525	1052
Mean (SD)	67.9 (8.42)	68.9 (8.11)	68.4 (8.28)
Median	68.0	69.0	68.0
Range	(43; 90)	(45; 94)	(43; 94)
<65	182 (34.5%)	149 (28.4%)	331 (31.5%)
65-69	108 (20.5%)	136 (25.9%)	244 (23.2%)
70-74	124 (23.5%)	107 (20.4%)	231 (22.0%)
≥ 75	113 (21.4%)	133 (25.3%)	246 (23.4%)
Race			
N	527	525	1052
American Indian or Alaska Native	13 (2.5%)	6 (1.1%)	19 (1.8%)
Asian	110 (20.9%)	119 (22.7%)	229 (21.8%)
Black or African American	9 (1.7%)	10 (1.9%)	19 (1.8%)
White	365 (69.3%)	354 (67.4%)	719 (68.3%)
Other	22 (4.2%)	24 (4.6%)	46 (4.4%)
Multiple	0	1 (0.2%)	1 (0.1%)
Not reported	8 (1.5%)	11 (2.1%)	19 (1.8%)
Ethnicity			
N	527	525	1052
Hispanic or Latino	86 (16.3%)	88 (16.8%)	174 (16.5%)
Not Hispanic or Latino	428 (81.2%)	425 (81.0%)	853 (81.1%)
Not reported	7 (1.3%)	9 (1.7%)	16 (1.5%)
Unknown	6 (1.1%)	3 (0.6%)	9 (0.9%)
Weight, kg			
N	523	520	1043
Mean (SD)	78.41 (16.805)	78.27 (15.506)	78.34 (16.163)
Median	77.00	76.60	76.90
Range	(40.7; 157.0)	(40.0; 141.0)	(40.0; 157.0)
Height, cm			
N	524	519	1043
Mean (SD)	172.00 (7.954)	171.34 (7.981)	171.67 (7.971)
Median	172.00	171.00	171.60
Range	(147.0; 194.0)	(147.0; 198.1)	(147.0; 198.1)

Table 8: Disease characteristics at Diagnosis and Baseline; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide	Total
Analysis set: Intent-to-treat population	527	525	1052
Time from initial diagnosis to randomization (months)[a]			
Mean (SD)	11.29 (26.195)	15.12 (31.797)	13.20 (29.175)
Median	4.04	4.11	4.04
Range	(0.7; 341.4)	(0.5; 222.9)	(0.5; 341.4)
Time from metastatic diagnosis to randomization (months)[a]			
Mean (SD)	3.41 (2.430)	3.50 (2.971)	3.46 (2.712)
Median	2.69	2.63	2.66
Range	(0.4; 27.1)	(0.5; 28.2)	(0.4; 28.2)
Metastasis stage at diagnosis			
M0	59 (11.2%)	85 (16.2%)	144 (13.7%)
M1	441 (83.7%)	411 (78.3%)	852 (81.0%)
MX	27 (5.1%)	29 (5.5%)	56 (5.3%)
Gleason score at initial diagnosis			
<7	39 (7.4%)	41 (7.8%)	80 (7.6%)
7	130 (24.7%)	133 (25.3%)	263 (25.0%)
8	154 (29.2%)	161 (30.7%)	315 (29.9%)
9	174 (33.0%)	165 (31.4%)	339 (32.2%)
10	30 (5.7%)	25 (4.8%)	55 (5.2%)
BPI-SF Pain Score (worst pain over last 24 hours)[b]			
N	513	503	1016
Mean (SD)	1.84 (2.127)	1.93 (2.190)	1.89 (2.157)
Median	1.00	1.14	1.00
Range	(0.0; 9.4)	(0.0; 10.0)	(0.0; 10.0)
ECOG Performance Status Grade			
0	348 (66.0%)	328 (62.5%)	676 (64.3%)
1	178 (33.8%)	197 (37.5%)	375 (35.6%)
2	1 (0.2%)	0	1 (0.1%)
Prior docetaxel use			
No	472 (89.6%)	467 (89.0%)	939 (89.3%)
Yes	55 (10.4%)	58 (11.0%)	113 (10.7%)
Extent of disease at study entry		-	
Bone	527 (100.0%)	525 (100.0%)	1052 (100.0%)
Bone Only	269 (51.0%)	289 (55.0%)	558 (53.0%)
Lymph Node	219 (41.6%)	199 (37.9%)	418 (39.7%)
Visceral	72 (13.7%)	56 (10.7%)	128 (12.2%)
Lung	64 (12.1%)	47 (9.0%)	111 (10.6%)
Liver	13 (2.5%)	12 (2.3%)	25 (2.4%)
Soft Tissue	27 (5.1%)	22 (4.2%)	49 (4.7%)
Number of bone lesions at study entry			
<=10	331 (62.8%)	318 (60.6%)	649 (61.7%)
>10	196 (37.2%)	207 (39.4%)	403 (38.3%)
Subgroups of mCSPC[c]			
High volume	335 (63.6%)	325 (61.9%)	660 (62.7%)
Low volume	192 (36.4%)	200 (38.1%)	392 (37.3%)

ECOG = Eastern Cooperative Oncology Group.
[a] Time from initial diagnosis in months is defined from the date initial diagnosis to the date of randomization +1 divided by 30.4375. Time from metastatic diagnosis in weeks is defined from the date of metastatic diagnosis to the date of randomization +1 divided by 7.
[b] Based on the average of a maximum of the 7 records closest to the first dose using a window of 14 days prior with minimum of 1 day.
[c] High-volume mCSPC is defined as 1) visceral metastases and at least 1 bone lesion or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low-volume mCSPC is defined as the presence of bone lesion(s) not meeting the definition of high-volume mCSPC.

Patients were considered to be castration sensitive based upon a short length of time of prior treatment with ADT as well as the fact that >90% of patients in both arms had a decrease in PSA following initiation of ADT which was still observed at the start of study treatment.

Table 9: PSA results from initiation of ADT for mCSPC to first dose; intent-to-treat population (study 56021927PCR3002)

TEFPSA_PRE: PSA Results from Initiation of ADT for mCSPC to First Dose; Intent-to-treat Population (Study 56021927PCR3002)		
	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
PSA at initiation of ADT for mCSPC (ng/mL)		
N	490	486
Mean (SD)	331.82 (1092.042)	1529.78 (23874.807)
Median	67.73	72.88
Range	(0.0; 18349.7)	(0.1; 526000.0)
Subjects with decline after initiation of ADT for mCSPC	457 (93.3%)	455 (93.6%)
Maximum percent[b] decline		
N	483	477
Mean (SD)	-36.43 (701.765)	-71.13 (113.932)
Median	-92.50	-91.54
Range	(-100.0; 15212.3)	(-100.0; 2132.3)

[b] A negative percent indicates a decline in PSA, whereas a positive percent indicates that the subject never has a decline in PSA.
Note: Percent is based on subjects who have PSA at initiation of ADT for mCSPC for each treatment group (as denominator).

Prior prostate cancer therapies

Table 10: Prior Prostate Cancer Therapy; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide	Total
Analysis set: Intent-to-treat population	527	525	1052
Previous prostate cancer therapy			
N	527	525	1052
Prostatectomy or radiotherapy	79 (15.0%)	94 (17.9%)	173 (16.4%)
Prostatectomy only	27 (5.1%)	26 (5.0%)	53 (5.0%)
Radiotherapy only	39 (7.4%)	47 (9.0%)	86 (8.2%)
Both prostatectomy and radiotherapy	13 (2.5%)	21 (4.0%)	34 (3.2%)
Hormonal therapy	527 (100.0%)	525 (100.0%)	1052 (100.0%)
First generation anti-androgen	361 (68.5%)	352 (67.0%)	713 (67.8%)
GnRHa	489 (92.8%)	496 (94.5%)	985 (93.6%)
Bilateral Orchiectomy	40 (7.6%)	33 (6.3%)	73 (6.9%)
Docetaxel	55 (10.4%)	58 (11.0%)	113 (10.7%)
Vandetanib	0	1 (0.2%)	1 (0.1%)

GnRHa = gonadotropin releasing hormone analog.

Prior docetaxel was received by 11% of patients, 58 patients in the apalutamide + ADT arm and 55 patients in the placebo + ADT arm. These patients were required to have maintained a response to docetaxel of stable disease or better prior to randomization in the study. All patients were informed about the survival benefit of docetaxel for the mCSPC setting but deferred docetaxel either because the investigator did not feel that docetaxel was standard of care (SOC) (65%) or the patient refused docetaxel therapy (12%).

Among patients with prior docetaxel treatment, there were a higher proportion of patients in the apalutamide + ADT arm with negative prognostic features (e.g., higher ECOG score [1 vs 0] and presence of visceral disease): 35% of patients in the apalutamide + ADT arm compared to 27% of patients in the placebo + ADT arm had an ECOG score of 1; 16% of patients in the apalutamide + ADT arm compared to 11% of patients in the placebo + ADT arm had presence of visceral disease. Additionally, patients with prior docetaxel treatment in the apalutamide + ADT arm had a higher median PSA at baseline (0.93 ug/L, apalutamide + ADT arm and 0.57 ug/L, placebo + ADT arm) as well as higher mean alkaline phosphatase values at baseline (120 U/L, apalutamide + ADT arm and 95 U/L, placebo + ADT arm).

All patients had received hormonal therapy prior to randomization, usually a combination of anti-androgens and GnRH agonists. Most patients (71%) had received prior ADT for mCSPC for 3 months or less prior to randomization; the median length of time from initiation of ADT for mCSPC to randomization was 1.8 months. Two patients were documented as major protocol deviations with time from initiation of ADT to randomization of 105 months. Few patients (5.2%) received ADT in the localized setting.

Numbers analysed

Efficacy analyses were based on the ITT population of 1052 patients (525 patients in the apalutamide + ADT arm and 527 patients in the placebo + ADT arm).

Outcomes and estimation

Dual Primary endpoints

Overall survival

A statistically significant improvement in OS was demonstrated in patients randomised to receive apalutamide compared with patients randomised to receive placebo. The HR for OS was 0.67 (95% CI: 0.51, 0.89; p=0.0053), representing a 33% reduction in the risk of death for patients in the apalutamide + ADT arm compared with the placebo + ADT arm. The pre-specified alpha boundary of 0.0101 (Wang-Tsiatis power boundary with a shape parameter of 0.2) for this interim analysis (at approximately 50% OS events) was crossed. Median OS follow-up was approximately 22 months in both groups.

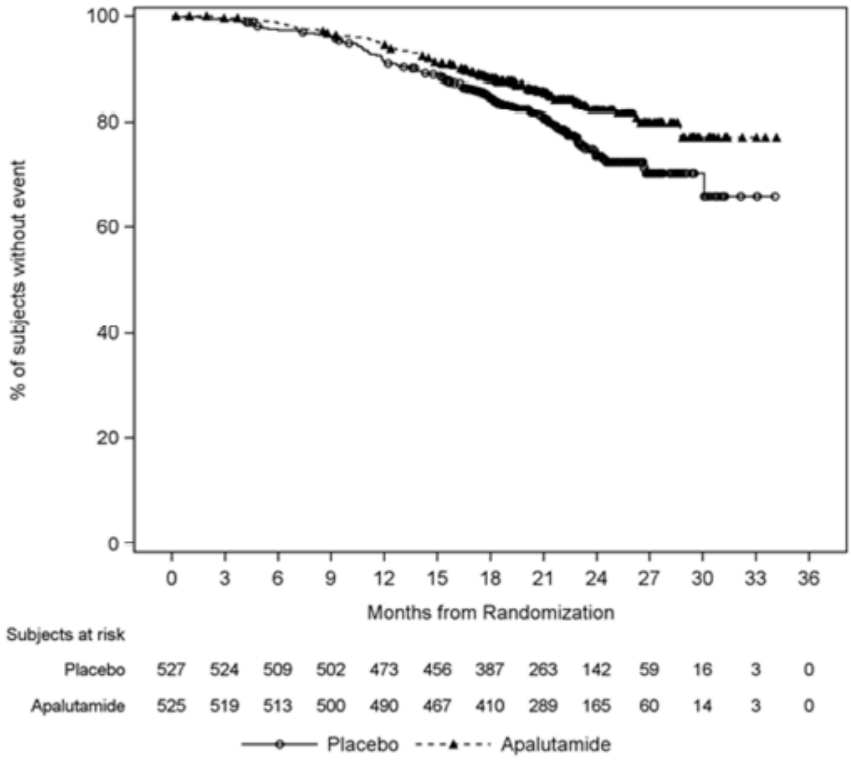
Table 11: Overall Survival - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	117 (22.2%)	83 (15.8%)
Censored	410 (77.8%)	442 (84.2%)
Time to event (months)		
25th percentile (95% CI)	23.36 (21.78, 30.06)	NE (26.32, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.4, 34.1+)	(0.2+, 34.2+)
6-month event-free rate (95% CI)	0.973 (0.955, 0.984)	0.987 (0.972, 0.994)
12-month event-free rate (95% CI)	0.912 (0.884, 0.933)	0.948 (0.925, 0.964)
24-month event-free rate (95% CI)	0.735 (0.687, 0.778)	0.824 (0.784, 0.858)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0053
Hazard ratio (95% CI)[b]		0.671 (0.507, 0.890)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

A non-stratified log rank test of OS was performed as a sensitivity analysis. The sensitivity analysis confirmed that treatment with apalutamide + ADT significantly prolonged OS compared with placebo + ADT (HR=0.68; 95%CI: 0.51, 0.90. p=0.0061).

Figure 8: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study 56021927PCR3002)



Radiographic Progression-free Survival

A statistically significant improvement in rPFS was demonstrated in patients randomised to receive Erleada compared with patients randomised to receive placebo. The HR for rPFS was 0.48 (95% CI: 0.39, 0.60; p<0.0001), representing a 52% reduction in the risk of radiographic progression or death for patients in the apalutamide + ADT arm compared with the placebo + ADT arm. The alpha boundary of 0.005 was crossed.

Table 12: Radiographic Progression-Free Survival (rPFS), Primary Analysis - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	231 (43.8%)	134 (25.5%)
Censored	296 (56.2%)	391 (74.5%)
Time to event (months)		
25th percentile (95% CI)	10.91 (8.71, 11.10)	18.43 (17.38, 22.11)
Median (95% CI)	22.08 (18.46, 32.92)	NE (NE, NE)
75th percentile (95% CI)	32.92 (30.49, NE)	NE (NE, NE)
Range	(0.0+, 33.1+)	(0.0+, 33.3+)
6-month event-free rate (95% CI)	0.870 (0.838, 0.896)	0.955 (0.932, 0.970)
12-month event-free rate (95% CI)	0.703 (0.660, 0.741)	0.843 (0.807, 0.873)
24-month event-free rate (95% CI)	0.475 (0.421, 0.528)	0.682 (0.629, 0.729)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.484 (0.391, 0.600)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

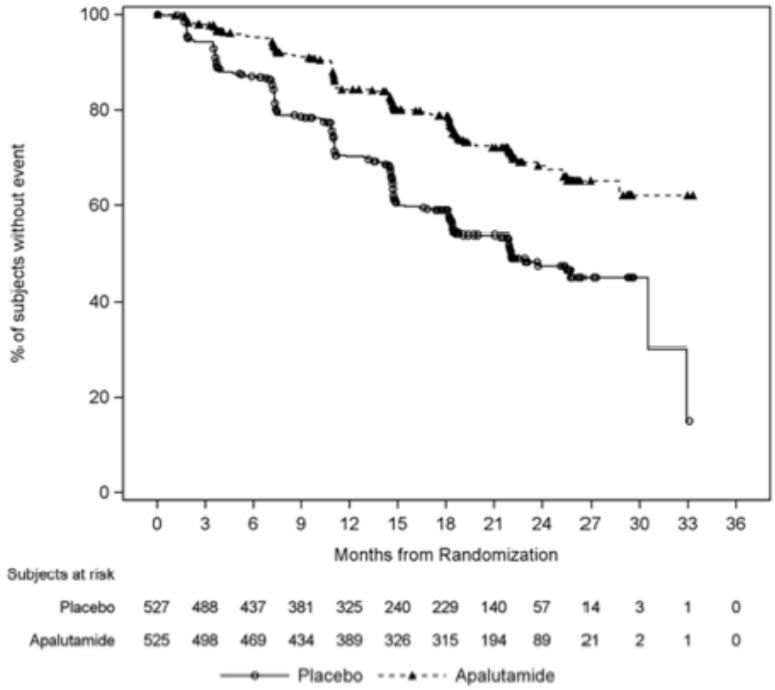


Figure 9: Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat Population (Study 56021927PCR3002)

Blinded independent central review (BICR) of radiographic progression was conducted in a randomly selected sample consisting of approximately 60% of patients in the study. The result of this subgroup analysis of rPFS by BICR was highly significant (p<0.0001) in favour of apalutamide. The primary audit analysis by the NCI method confirmed the investigator assessment. Furthermore, audit analysis also confirmed no investigator bias and the validity of the investigator results.

Table 13: Radiographic Progression-Free Survival (rPFS), (Central Review) - Stratified Analysis; Audit Patients (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Audit subjects	296	304
Event	122 (41.2%)	74 (24.3%)
Censored	174 (58.8%)	230 (75.7%)
Time to event (months)		
25th percentile (95% CI)	11.04 (7.49, 14.52)	18.69 (18.23, 22.14)
Median (95% CI)	22.97 (18.63, 32.92)	NE (28.71, NE)
75th percentile (95% CI)	32.92 (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.9)	(0.0+, 33.0+)
6-month event-free rate (95% CI)	0.879 (0.835, 0.911)	0.945 (0.912, 0.966)
12-month event-free rate (95% CI)	0.713 (0.656, 0.762)	0.852 (0.804, 0.889)
24-month event-free rate (95% CI)	0.497 (0.423, 0.567)	0.677 (0.603, 0.740)
36-month event-free rate (95% CI)	0.000 (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.507 (0.378, 0.680)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Table 14: Audit Analysis [NCI Method] of Radiographic Progression-free Survival based on Investigator Assessment and Central Review; Intent-to-treat Population (Study 56021927PCR3002)

	rPFS-LE	rPFS-LE (audited subjects)	rPFS-LE (non-audited subjects)	rPFS-BICR (audited subjects)	rPFS-BICR Overall Estimate
Analysis set: Intent-to-treat population	1052	600	452	600	
HR	0.484	0.592	0.364	0.507	0.434
(95% CI)	(0.391, 0.600)	(0.445, 0.788)	(0.261, 0.507)	(0.378, 0.680)	(0.335, 0.563)

Key: HR= hazard ratio; BICR=blinded independent central review; LE=Investigator or Local Site Evaluation; CI=confidence interval.
All estimates are based on stratified proportional hazards model.
If the upper limit of the overall HR by BICR is below 1, then the concordance between the LE and BICR will be confirmed.

For the purpose of sensitivity analysis only, a nadir bone scan was determined for each subject. A nadir bone scan was defined as the scan with the least visible evidence of disease based on the reviewers' judgement. Nadir scans were independently selected by the central reviewers as well as by investigators. The timepoint of the nadir scan was used to define a new baseline from which bone metastasis progression (≥2 new lesions) on subsequent bone scans were determined.

Table 15: Radiographic Progression-Free Survival (rPFS), Sensitivity Analysis Compared with Nadir Bone Scan, (Central Review) - Stratified Analysis; Audit Patients (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Audit subjects	296	304
Event	122 (41.2%)	74 (24.3%)
Censored	174 (58.8%)	230 (75.7%)
Time to event (months)		
25th percentile (95% CI)	10.97 (7.49, 14.42)	18.69 (14.78, 22.14)
Median (95% CI)	22.97 (18.63, 32.92)	NE (28.71, NE)
75th percentile (95% CI)	32.92 (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.9)	(0.0+, 33.0+)
6-month event-free rate (95% CI)	0.879 (0.835, 0.911)	0.945 (0.912, 0.966)
12-month event-free rate (95% CI)	0.702 (0.644, 0.752)	0.833 (0.783, 0.872)
24-month event-free rate (95% CI)	0.499 (0.425, 0.568)	0.673 (0.599, 0.737)
36-month event-free rate (95% CI)	0.000 (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.513 (0.383, 0.689)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Secondary endpoints

The analyses of secondary endpoints were ordered according to the hierarchical testing sequence as prespecified in the SAP. Time to cytotoxic chemotherapy was highly statistically significant. Time to pain progression was then tested but did not cross the boundary. As a result, the rest of the secondary endpoints were not formally tested, and only nominal p-values are provided.

Time to Initiation of Cytotoxic Chemotherapy

Treatment with Erleada statistically significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.391, CI = 0.274, 0.558; p < 0.0001), resulting in a 61% reduction of risk for subjects in the treatment arm compared to the placebo arm.

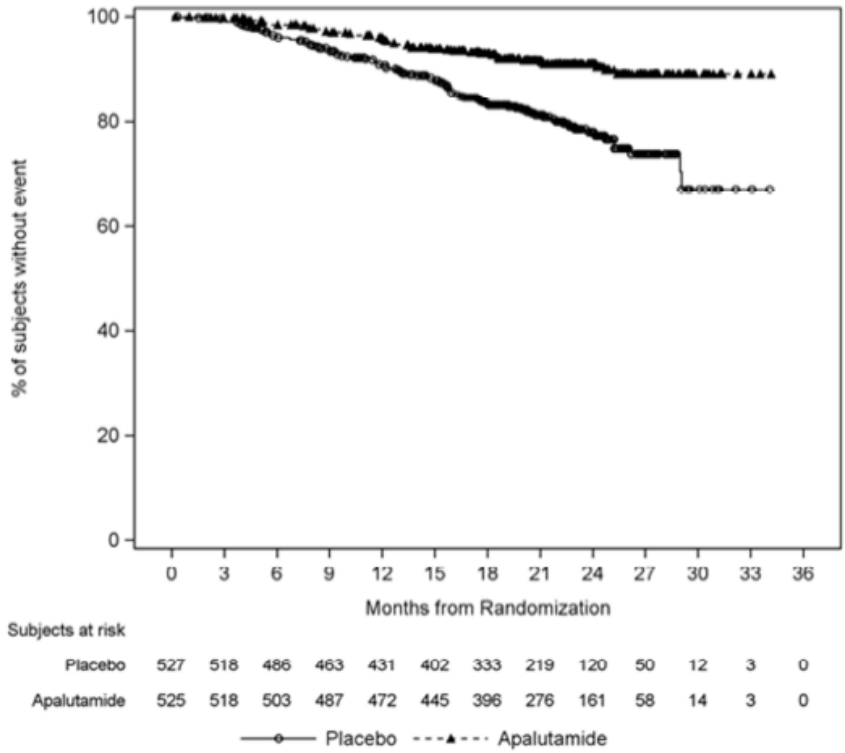
Of the patients who received subsequent chemotherapy, 89/100 patients in the placebo + ADT arm and 37/44 patients in the apalutamide + ADT arm received docetaxel. Most of these (67/89 patients in the placebo + ADT arm and 29/37 patients in the apalutamide + ADT arm) received docetaxel as the first systemic therapy for prostate cancer following discontinuation of study treatment (see Table 23).

Table 16: Time to Initiation of Cytotoxic Chemotherapy - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	100 (19.0%)	44 (8.4%)
Censored	427 (81.0%)	481 (91.6%)
Time to event (months)		
25th percentile (95% CI)	25.23 (22.60, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3+, 34.1+)	(0.2+, 34.2+)
6-month event-free rate (95% CI)	0.961 (0.940, 0.975)	0.984 (0.969, 0.992)
12-month event-free rate (95% CI)	0.908 (0.879, 0.930)	0.958 (0.937, 0.973)
24-month event-free rate (95% CI)	0.780 (0.734, 0.819)	0.912 (0.881, 0.934)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.391 (0.274, 0.558)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 10: Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy; Intent-to-treat Population (Study 56021927PCR3002)



Time to pain progression

The median pain score at baseline was 1 in both treatment arms. During the study, pain scores remained stable from baseline, with a low percentage of patients worsening by 1 point or ≥2 points and similar changes between groups.

Table 17: Time to Pain Progression (>=2-point Increase from Baseline to >4 with Minimum of 1 Day Data) - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	148 (28.1%)	128 (24.4%)
Censored	379 (71.9%)	397 (75.6%)
Time to event (months)		
25th percentile (95% CI)	14.78 (11.07, 19.81)	20.53 (16.10, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.2, 34.1+)	(0.1, 34.2+)
6-month event-free rate (95% CI)	0.872 (0.840, 0.898)	0.881 (0.850, 0.906)
12-month event-free rate (95% CI)	0.779 (0.740, 0.812)	0.825 (0.790, 0.856)
24-month event-free rate (95% CI)	0.696 (0.652, 0.736)	0.735 (0.691, 0.774)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.1173
Hazard ratio (95% CI)[b]		0.828 (0.653, 1.049)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Time to chronic opioid use

Natural opium alkaloids were taken by 11% of patients during the study (1.8% prior to study entry), other opioids by 11% (3% prior to study entry) and opioids in combination with non-opioid analgesics by 10% (2.3% prior to study entry).

Table 18: Time to Chronic Opioid Use - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	65 (12.3%)	52 (9.9%)
Censored	462 (87.7%)	473 (90.1%)
Time to event (months)		
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.2, 34.1+)	(0.1, 34.2+)
6-month event-free rate (95% CI)	0.958 (0.937, 0.972)	0.971 (0.953, 0.982)
12-month event-free rate (95% CI)	0.924 (0.897, 0.944)	0.945 (0.922, 0.962)
24-month event-free rate (95% CI)	0.860 (0.823, 0.890)	0.889 (0.855, 0.916)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.1635
Hazard ratio (95% CI)[b]		0.772 (0.536, 1.112)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Time to skeletal-related events

Fifty-three events (10%) were recorded in the apalutamide + ADT arm and 64 events (12%) were recorded in the placebo + ADT arm. Median time to skeletal-related events, favored treatment with apalutamide + ADT (HR=0.798, 95%CI: 0.555, 1.149). Nominal p value was 0.2246.

Table 19: Time to skeletal-related event (TTSRE) - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	64 (12.1%)	53 (10.1%)
Censored	463 (87.9%)	472 (89.9%)
Time to event (months)		
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.2, 34.1+)	(0.1, 33.5+)
6-month event-free rate (95% CI)	0.959 (0.938, 0.973)	0.965 (0.946, 0.978)
12-month event-free rate (95% CI)	0.917 (0.889, 0.938)	0.946 (0.922, 0.962)
24-month event-free rate (95% CI)	0.867 (0.830, 0.896)	0.886 (0.851, 0.912)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.2246
Hazard ratio (95% CI)[b]		0.798 (0.555, 1.149)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Other efficacy endpoints

Time to PSA progression

Table 20: Time to PSA Progression (based on PCWG2 criteria) - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	302 (57.3%)	109 (20.8%)
Censored	225 (42.7%)	416 (79.2%)
Time to event (months)		
25th percentile (95% CI)	5.55 (4.63, 6.47)	22.21 (18.43, NE)
Median (95% CI)	12.91 (10.18, 14.75)	NE (NE, NE)
75th percentile (95% CI)	NE (29.47, NE)	NE (NE, NE)
Range	(0.0+, 33.1+)	(0.0+, 33.3+)
6-month event-free rate (95% CI)	0.729 (0.688, 0.766)	0.939 (0.914, 0.957)
12-month event-free rate (95% CI)	0.519 (0.474, 0.562)	0.855 (0.820, 0.884)
24-month event-free rate (95% CI)	0.362 (0.316, 0.407)	0.747 (0.700, 0.789)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.259 (0.207, 0.323)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

A maximal decline in PSA values of 90% or greater from baseline was recorded for 74% of patients receiving apalutamide + ADT and 27% of patients in the placebo + ADT arm.

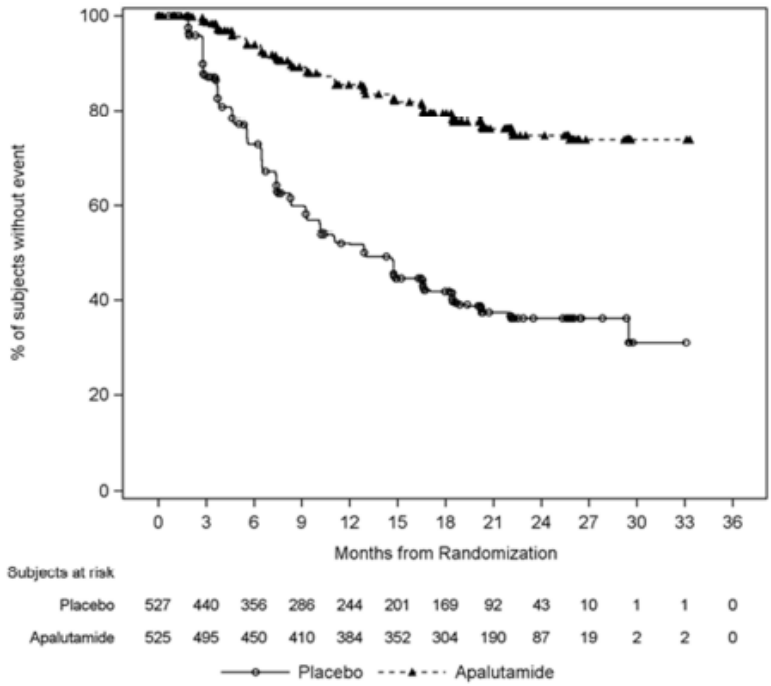


Figure 11: Kaplan-Meier Plot of Time to PSA Progression; Intent-to-treat Population (Study 56021927PCR3002)

PFS2

Table 21: Second Progression-Free Survival (PFS2) - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Event	121 (23.0%)	88 (16.8%)
Censored	406 (77.0%)	437 (83.2%)
Time to event (months)		
25th percentile (95% CI)	22.93 (20.34, 26.78)	NE (26.09, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.4, 34.1+)	(0.2+, 34.2+)
6-month event-free rate (95% CI)	0.971 (0.953, 0.983)	0.981 (0.965, 0.990)
12-month event-free rate (95% CI)	0.899 (0.870, 0.922)	0.942 (0.918, 0.959)
24-month event-free rate (95% CI)	0.717 (0.667, 0.762)	0.813 (0.772, 0.848)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0026
Hazard ratio (95% CI)[b]		0.657 (0.499, 0.865)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

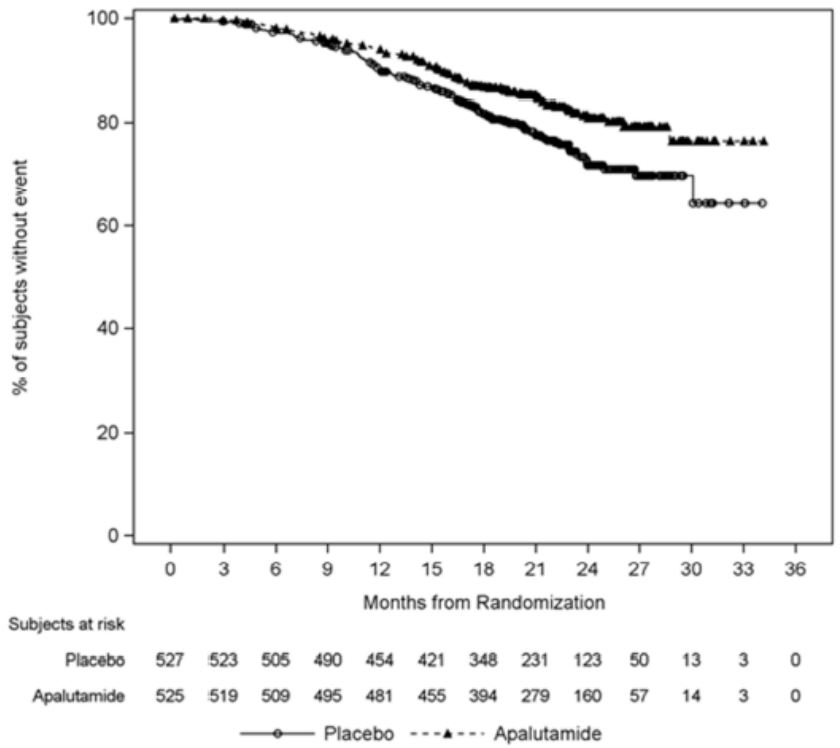


Figure 12: Kaplan-Meier Plot of Second Progression-Free Survival (PFS2); Intent-to-treat Population (Study 56021927PCR3002)

Best overall response (exploratory post-hoc analysis)

Complete response, based on modified RECIST criteria assessing visceral, soft tissue, and lymph nodes, was 27% in the apalutamide + ADT arm and 19% in the placebo + ADT arm. Responders, including complete or partial responses, were 72% and 64%, respectively.

Table 22: Best Overall Response Based on RECIST [Version 1.1]; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Number of subjects with measurable disease at baseline	134	140
Best Overall Response		
Complete Response	26 (19.4%)	38 (27.1%)
Partial Response	60 (44.8%)	63 (45.0%)
Stable Disease	37 (27.6%)	28 (20.0%)
Progressive Disease	7 (5.2%)	9 (6.4%)
Not Evaluable	4 (3.0%)	2 (1.4%)

Note: CR and PR do not have to be confirmed.

PRO analyses

The cumulative compliance rate was similar between treatment arms for the completion of the BPI-SF and BFI, with greater than 96% through Cycle 13. After Cycle 13, the cumulative compliance rate was generally within 90% or greater for cycles associated with a clinic visit. Lower compliance was observed for cycles completed at home without a clinic visit (ranging from 75% to 85%).

Cumulative compliance rate for the FACT-P and EQ-5D-5L, completed one time per cycle visit, was generally similar between treatment groups. From baseline through Cycle 13, the compliance rate ranged from 75% to 85%. After Cycle 13, compliance for the majority of visits were within the range of 80%.

Compliance rates in the Follow-up Phase were lower for all PROs in both treatment groups. For BPI and BFI overall compliance was 49% at Month 4, 42% at Month 8 and 30% at Month 12. For FACT-P and EQ-5D-5L overall compliance was 32% at Month 4, 32% at Month 8, and 20% at Month 12.

Assessment of the PRO data from TITAN showed that patients entering this study were relatively asymptomatic, with low median pain and fatigue intensity at baseline. Pain and fatigue levels as well as pain interference and fatigue interference remained similar between treatment groups throughout the treatment phase. Post-hoc analysis of the proportion of responses to the pain intensity item showed that the majority of the patients' pain intensity scores remained stable or improved.

There were no changes from baseline in the FACT-P in the apalutamide + ADT treatment arm (cycle 25, LS Means 0.50) and no differences compared to ADT (p=0.2367). There were no statistically significant differences observed between treatment groups for the FACT-P overall, or the EQ5D-5L.

Ancillary analyses

Subsequent therapy

Of patients who discontinued study treatment for any reason and were still alive, more patients in the placebo + ADT arm (73%) received subsequent therapy for prostate cancer compared with the apalutamide + ADT arm (54%). Of patients who discontinued study treatment due to progressive disease and were still alive, 78% of patients in the placebo + ADT arm and 70% of patients in the apalutamide + ADT arm received subsequent therapy for prostate cancer.

Table 23: Subsequent Therapy for Prostate Cancer; Intent-to-treat Population (Study56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Number of subjects alive at treatment discontinuation (denominator for table below)	271	170
Number of subjects with subsequent therapy for prostate cancer	197 (72.7%)	92 (54.1%)
Radiotherapy	43 (15.9%)	21 (12.4%)
Surgery	10 (3.7%)	9 (5.3%)
Hormonal	132 (48.7%)	53 (31.2%)
Abiraterone	69 (25.5%)	30 (17.6%)
Bicalutamide	37 (13.7%)	19 (11.2%)
Enzalutamide	35 (12.9%)	10 (5.9%)
Flutamide	6 (2.2%)	3 (1.8%)
Diethylstilbestrol	0	2 (1.2%)
Chlormadinone Acetate	0	1 (0.6%)
Nilutamide	0	1 (0.6%)
Chlorotrianisene	1 (0.4%)	0
Cyproterone	3 (1.1%)	0
Methylprednisolone	1 (0.4%)	0
Cytotoxic chemotherapy	100 (36.9%)	44 (25.9%)
Docetaxel	89 (32.8%)	37 (21.8%)
Cabazitaxel	18 (6.6%)	6 (3.5%)
Carboplatin	6 (2.2%)	6 (3.5%)
Paclitaxel	1 (0.4%)	4 (2.4%)
Etoposide	3 (1.1%)	3 (1.8%)
Capecitabine	0	1 (0.6%)
Estramustine	3 (1.1%)	1 (0.6%)
Cabazitaxel Acetone	1 (0.4%)	0
Cisplatin	2 (0.7%)	0
Cyclophosphamide	1 (0.4%)	0
Gemcitabine	1 (0.4%)	0
Lobaplatin	1 (0.4%)	0
Mitoxantrone	2 (0.7%)	0
Other	75 (27.7%)	31 (18.2%)
Zoledronic	16 (5.9%)	9 (5.3%)
Prednisolone	16 (5.9%)	6 (3.5%)
Prednisone	27 (10.0%)	6 (3.5%)
Radium-223	10 (3.7%)	6 (3.5%)
Dexamethasone	3 (1.1%)	5 (2.9%)
Sipuleucel-T	6 (2.2%)	2 (1.2%)
Clodronate	1 (0.4%)	1 (0.6%)
Denosumab	0	1 (0.6%)
Ibandronic Acid	0	1 (0.6%)
Investigational Antineoplastic Drugs	0	1 (0.6%)
Masitinib	1 (0.4%)	1 (0.6%)
Atezolizumab	1 (0.4%)	0
Cabozantinib	1 (0.4%)	0
Investigational Drug	2 (0.7%)	0
Ketoconazole	1 (0.4%)	0
Meprednisone	1 (0.4%)	0
Nivolumab	1 (0.4%)	0
Pegfilgrastim	1 (0.4%)	0
Pembrolizumab	2 (0.7%)	0
Poly Adp-Ribose Polymerase Inhibitor	1 (0.4%)	0

Note: Continuing ADT is not considered as a subsequent therapy.

Table 24: Selected Subsequent Therapy for Prostate Cancer; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	527	525
Discontinued study treatment	284	177
Number of subjects alive at treatment discontinuation (denominator for table below)	271	170
Number of subjects with selected subsequent therapy for prostate cancer	165 (60.9%)	64 (37.6%)
Docetaxel	89 (32.8%)	37 (21.8%)
Abiraterone	69 (25.5%)	30 (17.6%)
Enzalutamide	35 (12.9%)	10 (5.9%)
Cabazitaxel	18 (6.6%)	6 (3.5%)
Radium-223	10 (3.7%)	6 (3.5%)
Sipuleucel-T	6 (2.2%)	2 (1.2%)
Cabazitaxel Acetone	1 (0.4%)	0

Subgroup analyses

Overall survival

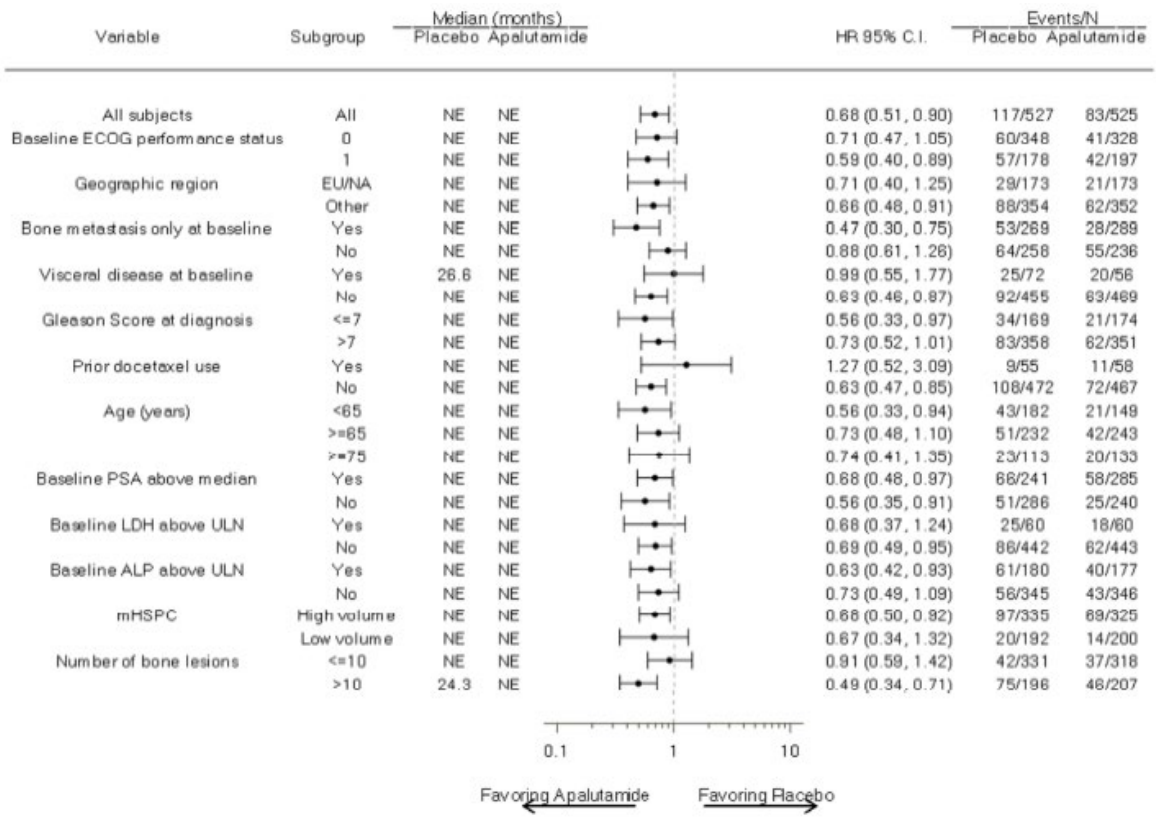


Figure 13: Forest Plot of Overall Survival; Intent-to-treat Population (Study 56021927PCR3002)

rPFS

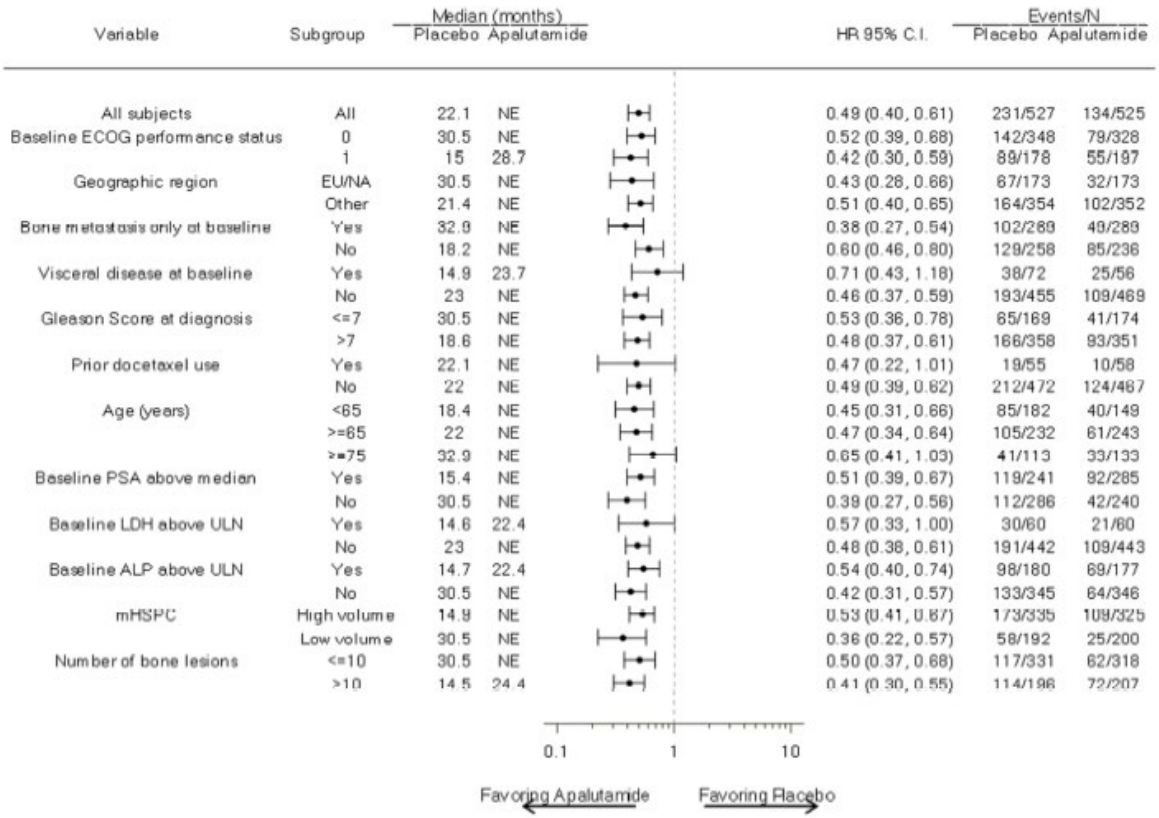


Figure 14: Forest Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat Population (Study 56021927PCR3002)

<u>Disease risk</u>

Additional analyses were done to evaluate the OS and rPFS for high and low-risk patients from the TITAN study. High-risk was defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥8; (2) presence of 3 or more lesions on bone scan; (3) (3) presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI scan (according to RECIST 1.1 criteria).

Overall survival

Table 25: Overall Survival, high risk patients - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	286	289
Event	84 (29.4%)	59 (20.4%)
Censored	202 (70.6%)	230 (79.6%)
Time to event (months)		
25th percentile (95% CI)	21.03 (17.87, 22.80)	26.15 (21.39, NE)
Median (95% CI)	30.06 (26.64, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (30.06, NE)	NE (NE, NE)
Range	(1.6, 32.1+)	(2.0+, 34.2+)
6-month event-free rate (95% CI)	0.972 (0.945, 0.986)	0.983 (0.959, 0.993)
12-month event-free rate (95% CI)	0.869 (0.823, 0.903)	0.937 (0.903, 0.960)
24-month event-free rate (95% CI)	0.628 (0.550, 0.696)	0.763 (0.700, 0.815)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0082
Hazard ratio (95% CI)[b]		0.639 (0.457, 0.893)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Table 26: Overall Survival, low risk patients - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	241	236
Event	33 (13.7%)	24 (10.2%)
Censored	208 (86.3%)	212 (89.8%)
Time to event (months)		
25th percentile (95% CI)	NE (NE, NE)	NE (28.71, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.4, 34.1+)	(0.2+, 33.5+)
6-month event-free rate (95% CI)	0.975 (0.945, 0.989)	0.991 (0.966, 0.998)
12-month event-free rate (95% CI)	0.962 (0.929, 0.980)	0.961 (0.927, 0.980)
24-month event-free rate (95% CI)	0.845 (0.785, 0.889)	0.895 (0.843, 0.930)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.1881
Hazard ratio (95% CI)[b]		0.703 (0.415, 1.191)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

rPFS

Table 27: Radiographic Progression-Free Survival (rPFS), low risk patients - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	241	236
Event	79 (32.8%)	46 (19.5%)
Censored	162 (67.2%)	190 (80.5%)
Time to event (months)		
25th percentile (95% CI)	14.75 (14.59, 21.85)	25.33 (18.69, NE)
Median (95% CI)	30.49 (25.56, NE)	NE (NE, NE)
75th percentile (95% CI)	32.92 (30.49, NE)	NE (NE, NE)
Range	(0.0+, 33.1+)	(0.0+, 33.0+)
6-month event-free rate (95% CI)	0.910 (0.866, 0.941)	0.973 (0.942, 0.988)
12-month event-free rate (95% CI)	0.834 (0.779, 0.876)	0.907 (0.860, 0.939)
24-month event-free rate (95% CI)	0.600 (0.516, 0.675)	0.750 (0.673, 0.812)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0006
Hazard ratio (95% CI)[b]		0.530 (0.367, 0.766)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Table 28: Radiographic Progression-Free Survival (rPFS), high risk patients - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	286	289
Event	152 (53.1%)	88 (30.4%)
Censored	134 (46.9%)	201 (69.6%)
Time to event (months)		
25th percentile (95% CI)	7.39 (7.20, 10.41)	14.75 (11.14, 18.43)
Median (95% CI)	14.85 (14.55, 18.23)	NE (25.56, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 29.5+)	(0.0+, 33.3+)
6-month event-free rate (95% CI)	0.837 (0.789, 0.875)	0.939 (0.904, 0.962)
12-month event-free rate (95% CI)	0.592 (0.530, 0.648)	0.791 (0.737, 0.835)
24-month event-free rate (95% CI)	0.366 (0.298, 0.435)	0.626 (0.550, 0.693)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.429 (0.329, 0.561)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Disease status at diagnosis

The TITAN study included patients who were de novo metastatic (M1 at initial diagnosis) or who developed metastases after initial diagnosis of localized disease (M0 at initial diagnosis).

Overall survival

Table 29 Overall Survival (OS), Patients with Metastasis stage at diagnosis of M0 – Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	59	85
Event	11 (18.6%)	7 (8.2%)
Censored	48 (81.4%)	78 (91.8%)
Time to event (months)		
25th percentile (95% CI)	NE (17.94, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(6.0, 29.5+)	(1.0+, 30.7+)
6-month event-free rate (95% CI)	0.983 (0.886, 0.998)	0.988 (0.918, 0.998)
12-month event-free rate (95% CI)	0.949 (0.851, 0.983)	0.988 (0.918, 0.998)
24-month event-free rate (95% CI)	0.776 (0.617, 0.876)	0.900 (0.792, 0.953)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0297
Hazard ratio (95% CI)[b]		0.325 (0.112, 0.943)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Table 30: Overall Survival (OS), Patients with Metastasis stage at diagnosis of M1 – Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	441	411
Event	101 (22.9%)	71 (17.3%)
Censored	340 (77.1%)	340 (82.7%)
Time to event (months)		
25th percentile (95% CI)	23.36 (21.39, 26.78)	28.71 (26.15, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.4, 34.1+)	(0.2+, 34.2+)
6-month event-free rate (95% CI)	0.973 (0.952, 0.984)	0.985 (0.968, 0.993)
12-month event-free rate (95% CI)	0.910 (0.879, 0.934)	0.938 (0.910, 0.958)
24-month event-free rate (95% CI)	0.729 (0.675, 0.775)	0.812 (0.765, 0.850)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0252
Hazard ratio (95% CI)[b]		0.707 (0.522, 0.959)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

rPFS

Table 31: Radiographic Progression-Free Survival (rPFS), Patients with Metastasis stage at diagnosis of M0 - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	59	85
Event	23 (39.0%)	17 (20.0%)
Censored	36 (61.0%)	68 (80.0%)
Time to event (months)		
25th percentile (95% CI)	7.36 (3.52, 13.73)	22.11 (14.72, NE)
Median (95% CI)	NE (13.73, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 29.3+)	(0.0+, 29.4+)
6-month event-free rate (95% CI)	0.809 (0.681, 0.889)	0.975 (0.905, 0.994)
12-month event-free rate (95% CI)	0.655 (0.512, 0.765)	0.878 (0.778, 0.935)
24-month event-free rate (95% CI)	0.563 (0.413, 0.688)	0.725 (0.583, 0.826)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value[a]		0.0056
Hazard ratio (95% CI)[b]		0.413 (0.216, 0.787)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Table 32: Radiographic Progression-Free Survival (rPFS), Patients with Metastasis stage at diagnosis of M1 - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Intent-to-treat population	441	411
Event	196 (44.4%)	108 (26.3%)
Censored	245 (55.6%)	303 (73.7%)
Time to event (months)		
25th percentile (95% CI)	11.01 (10.18, 13.04)	18.43 (16.10, 22.18)
Median (95% CI)	22.05 (18.43, 25.79)	NE (NE, NE)
75th percentile (95% CI)	32.92 (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.9)	(0.0+, 33.3+)
6-month event-free rate (95% CI)	0.887 (0.853, 0.913)	0.950 (0.923, 0.967)
12-month event-free rate (95% CI)	0.712 (0.665, 0.753)	0.840 (0.800, 0.874)
24-month event-free rate (95% CI)	0.459 (0.399, 0.518)	0.677 (0.616, 0.730)
36-month event-free rate (95% CI)	0.000 (NE, NE)	NE (NE, NE)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.483 (0.381, 0.613)

[a] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

<u>Prognosis factors</u>

Overall survival

After adjusting for multiple covariates, treatment with apalutamide + ADT remained highly statistically significant and consistent with the primary OS analysis results, with a 38% reduction in risk of death compared with placebo + ADT (HR=0.617; 95% CI: 0.46, 0.83; p=0.0016).

The prognostic characteristics that appeared to influence OS at the p<0.05 level, in order from most effect to least, regardless of treatment group were: LDH, presence of visceral disease, number of bone lesions, PSA, and ECOG grade. Prior docetaxel treatment and age did not impact OS. Increased PSA and LDH are associated with decreased OS. Absence of baseline visceral disease and number of bone lesion (≤10) were associated with better OS.

Table 33: Overall Survival (OS) - Multivariate Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Model Fit		Hazard Ratio	
Model Parameter	Coeff. (SE)	p-value	Estimate	95% C.I.
Treatment (Apalutamide vs. Placebo)	-0.482 (0.153)	0.0016	0.617	(0.457,0.834)
PSA	0.104 (0.035)	0.0028	1.110	(1.036,1.189)
Lactate dehydrogenase	1.544 (0.261)	<.0001	4.685	(2.809,7.812)
Alkaline phosphatase	0.009 (0.109)	0.9309	1.010	(0.815,1.250)
Hemoglobin	-0.005 (0.005)	0.3737	0.995	(0.985,1.006)
Average Pain score at baseline	0.052 (0.033)	0.1121	1.053	(0.988,1.123)
Age	0.000 (0.009)	0.9941	1.000	(0.982,1.019)
ECOG grade (0 vs. 1)	-0.438 (0.161)	0.0065	0.645	(0.471,0.884)
Number of bone lesions at baseline (<=10 vs. >10)	-0.737 (0.191)	0.0001	0.478	(0.329,0.695)
Presence of visceral disease (no vs. yes)	-0.763 (0.181)	<.0001	0.466	(0.327,0.664)
Receipt of localized therapy (no vs. yes)	-0.244 (0.281)	0.3849	0.783	(0.451,1.359)
Geographic region (NA/EU vs. other countries)	-0.095 (0.197)	0.6305	0.910	(0.618,1.338)
Gleason score (<=7 vs. >7)	-0.313 (0.168)	0.0628	0.731	(0.525,1.017)
Prior docetaxel use (no vs. yes)	0.100 (0.300)	0.7388	1.105	(0.614,1.990)

Model dependent variable is overall survival, expressed as days from date of randomization to date of death from any cause.
If the hazard ratio < 1, then result favors the first level of the parameter (as listed above).
Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.
The logarithmic value of PSA, Lactate dehydrogenase and Alkaline phosphatase is used.
All factors included in the table are baseline factors.

rPFS

After adjusting for multiple covariates, treatment with apalutamide + ADT remained highly statistically significant and consistent with the primary rPFS analysis results; with a 57% reduction in risk compared with placebo + ADT (HR=0.432; 95% CI: 0.34, 0.54; p-value <0.0001). Prognostic characteristics that appeared to influence rPFS at the p<0.05 level, regardless of treatment group were: LDH, presence of visceral disease, number of bone lesions, PSA, and age. Elevated PSA and LDH were associated with decreased rPFS. The absence of visceral disease, fewer bone lesions (≤10), and younger age were associated with improved rPFS.

Table 34: Radiographic Progression-Free Survival (rPFS) - Multivariate Analysis; Intent-to-treat Population (Study 56021927PCR3002)

	Model Fit		Hazard Ratio	
Model Parameter	Coeff. (SE)	p-value	Estimate	95% C.I.
Treatment (Apalutamide vs. Placebo)	-0.840 (0.115)	<.0001	0.432	(0.344,0.541)
PSA	0.091 (0.025)	0.0002	1.095	(1.043,1.150)
Lactate dehydrogenase	0.883 (0.219)	<.0001	2.419	(1.575,3.716)
Alkaline phosphatase	0.055 (0.084)	0.5178	1.056	(0.895,1.246)
Hemoglobin	-0.006 (0.004)	0.1492	0.994	(0.987,1.002)
Average Pain score at baseline	0.021 (0.025)	0.3979	1.022	(0.972,1.073)
Age	-0.017 (0.007)	0.0130	0.983	(0.969,0.996)
ECOG grade (0 vs. 1)	-0.123 (0.120)	0.3068	0.884	(0.698,1.120)
Number of bone lesions at baseline (<=10 vs. >10)	-0.629 (0.138)	<.0001	0.533	(0.407,0.699)
Presence of visceral disease (no vs. yes)	-0.499 (0.146)	0.0006	0.607	(0.456,0.809)
Receipt of localized therapy (no vs. yes)	-0.340 (0.219)	0.1201	0.711	(0.463,1.093)
Geographic region (NA/EU vs. other countries)	0.024 (0.139)	0.8646	1.024	(0.780,1.344)
Gleason score (<=7 vs. >7)	-0.233 (0.120)	0.0521	0.792	(0.627,1.002)
Prior docetaxel use (no vs. yes)	0.389 (0.230)	0.0906	1.475	(0.940,2.314)

Model dependent variable is rPFS, expressed as days from date of randomization to date of rPFS from any cause. If the hazard ratio < 1, then result favors the first level of the parameter (as listed above).
Subjects who do not have a rPFS event at time of analysis are censored on the last disease assessment date subject was known to have no PD or lost to follow-up.
The logarithmic value of PSA, Lactate dehydrogenase and Alkaline phosphatase is used.
All factors included in the table are baseline factors.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35: Summary of Efficacy for trial 56021927PCR3002 (TITAN)

Title: Randomized, placebo-controlled, double-blind study of apalutamide plus androgen deprivation therapy (ADT) versus ADT in patients with metastatic hormone-sensitive prostate cancer (mHSPC)		
Study identifier	Protocol 56021927PCR3002; Phase 3; EudraCT Number: 2015-000735-32	
Design	Randomized, double-blind, placebo-controlled, multinational, and multicenter Phase 3 study to determine if patients with mHSPC will benefit from the addition of apalutamide to ADT	
	Duration of screening phase: Duration of treatment phase: Duration of follow-up phase: Open-label Extension phase:	Up to 28 days before randomization 28-day treatment cycles Data collection every 4 months until death, withdrawal of consent, lost to follow-up or termination of the study Active drug for approx. 3 years
Hypothesis	Superiority: Apalutamide plus ADT compared with ADT alone will improve rPFS or OS or both and have an acceptable safety profile in patients with mHSPC	
Treatments groups	ADT + Apa	Apa 240 mg once daily +ADT
	ADT	Placebo + ADT

Endpoints and definitions	Dual-Primary endpoint	**rPFS & OS**	rPFS: time from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first. Radiographic progression will be assessed by soft tissue lesion by CT/MRI per modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or by bone lesion progression on bone scans. OS: time from randomization to the date of death from any cause.
	Secondary:	Time to initiation of cytotoxic chemotherapy	Time from date of randomization to the date of initiation of cytotoxic chemotherapy
	Secondary:	Time to pain progression	Time from the date of randomization to the date of the first observation of pain progression (increase by 2 points from baseline in the BPI-SF worst pain intensity [item 3] observed at 2 consecutive evaluations ≥4 weeks apart; with an average worst pain score of >4 in patients who have had no decrease in opioids or initiation of chronic opioids, whichever occurs first)
	Secondary:	Time to SRE	Time from the date of randomization to the date of the first observation of an SRE (occurrence of symptomatic pathological fracture, spinal cord compression, radiation to bone, or surgery to bone)
	Secondary:	Time to chronic opioid use	Time from date of randomization to the first date of confirmed chronic opioid use
Database lock	23 November 2018 (clinical cut-off date) for the investigator-assessed primary analysis of rPFS and the first interim analysis of OS		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	ADT + Apa	ADT
	Number of patients	525	527
	rPFS **Median (months)**	**NE**	**22.08**
	(95% CI)	**(NE, NE)**	**(18.46, 32.92)**
	OS **Median (months)**	**NE**	**NE**
	(95% CI)	**(NE, NE)**	**(NE, NE)**
	Time to initiation of cytotoxic chemotherapy Median (months)	NE	NE
	(95% CI)	(NE, NE)	(NE, NE)
	Time to pain progression Median (months)	NE	NE
	(95% CI)	(NE, NE)	(NE, NE)

Effect estimate per comparison	Dual-Primary **rPFS**	Comparison groups	<1 favors Apa+ADT
		Hazard ratio	**0.484**
		(95% CI)	**(0.391, 0.600)**
		P-value	<0.0001
	Dual-Primary **OS**	Comparison groups	<1 favors Apa+ADT
		Hazard ratio	**0.671**
		(95% CI)	**(0.507, 0.890)**
		P-value	0.0053
	Secondary: Time to initiation of cytotoxic chemotherapy	Comparison groups	<1 favors Apa+ADT
		Hazard ratio	0.391
		(95% CI)	(0.274, 0.558)
		P-value	<0.0001

	Secondary: Time to pain progression	Comparison groups	<1 favors Apa+ADT
		Hazard ratio	0.828
		(95% CI)	(0.653, 1.049)
		P-value	0.1173
	Secondary: Time to chronic opioid use	Comparison groups	<1 favors Apa+ADT
		Hazard ratio	0.772
		(95% CI)	(0.536, 1.112)
		P-value	0.1635
	Secondary: Time to skeletal-related event	Comparison groups	<1 favors Apa+ADT
		Hazard ratio	0.798
		(95% CI)	(0.555, 1.149)
		P-value	0.2246

Notes: The statistical testing of the secondary endpoints was performed by at the time of the first interim analysis using fixed sequence testing according to the following pre-specified order: time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to SRE. Time to cytotoxic chemotherapy was statistically significant. Time to pain progression was then tested but did not cross the boundary. As a result, the rest of the secondary endpoints were not formally tested, and only nominal p-values are provided.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The posology of apalutamide for the proposed indication (mCSPC) is in line with the currently approved indication (NM-CRPC) which was considered acceptable by the CHMP, since a positive benefit risk balance was agreed in the same disease.

The MAH presented results from study 56029127PCR3002 (TITAN), a Phase 3 randomized, placebo-controlled, double-blind study of apalutamide plus ADT versus ADT alone in 1,051 patients with mHSPC.

Study participants were eligible if there was a diagnosis (newly or previously diagnosed) of prostate adenocarcinoma as confirmed by the investigator and had metastatic disease with at least ≥1 bone lesion(s). Patients with lymph nodes or visceral metastases as the only sites of metastases were excluded from the trial. No patients with ECOG 2 or prior therapy with new hormonal treatments (abiraterone and enzalutamide) were allowed. On the contrary, prior docetaxel treatment was permitted provided only a maximum of 6 cycles was administered. The latter is following the findings from the CHAARTED trial. In this regard, both patients with high and low volume disease could be recruited in the TITAN study. High-volume mHSPC was correctly defined as 1) visceral metastases and at least 1 bone lesion or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low-volume mHSPC is defined as the presence of bone lesion(s) not meeting the definition of high-volume mHSPC.

Patients were randomized in a 1:1 ratio to the apalutamide (240 mg once daily) + ADT arm or matching placebo + ADT arm. Even if the design of this study was supported by the CHMP scientific advice given to the MAH (EMEA/H/SAH/031/1/2014/II), it would have been desirable and much more informative to use docetaxel as comparator, especially since Docetaxel's results were publicly available in 2014 (ASCO, NEJM).

Both, rPFS and OS were included as dual primary endpoints, which means either rPFS or OS positive results are enough to declare the success of the trial. Regarding the scanning frequency for rPFS, radiographic scans were obtained at screening (within 6 weeks prior to randomization), start of Cycle 3 (Week 8), Cycle 5 (Week 16), and then every 4 cycles (16 weeks) thereafter. However, gonadotropin hormone releasing analogs when first initiated may stimulate a bone flare response, which could be taken like tumor progression (false positive). In order to disentangle the tumour flare driven by ADT from a true bone progression, radiographic disease progression on bone scans within the first 12 weeks on study

required the appearance of ≥2 new lesions not consistent with tumour flare and was to be confirmed on a second bone scan ≥6 weeks later that shows a minimum of ≥2 additional new lesions.

Secondary endpoints included time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to Skeletal-related event which are considered relevant and acceptable.

Patients were stratified by Gleason score at diagnosis (≤7 versus >7), region (North America [NA] and European Union [EU] versus Other Countries), and prior docetaxel use (Yes versus No). Gleason score and prior docetaxel use are deemed to be important prognostic factors and therefore rightly chosen as stratification factors.

Overall, the statistical methods are deemed appropriate, with ITT as the primary analysis population. Importantly, as per the SAP, the statistical testing of the secondary endpoints was to be performed by using fixed sequence testing according to the following pre-specified order considering clinical importance and data maturity: time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to SRE.

The strategies to maintain the study integrity with regards to the randomization codes was discussed. According to applicant's justification, the integrity of randomization codes was kept. Before the unblinding of the study team (28 January 2019), 15 patients were unblinded at the request of the Investigator. In accordance with Section 5 of the Protocol these were done after the patients had achieved rPFS and met criteria for withdrawal. None of the patients were unblinded to resolve an urgent safety event, they were unblinded to obtain information to inform subsequent treatment.

The final SAP (version 1.0) was approved on 10 January 2019, prior to the final database lock or data extraction (14 January 2019) but after the clinical data cut-off (23 November 2018, when the required number of events for the interim OS analysis had occurred). According to applicant's justification, a draft SAP had been available since 22 August 2016 and was updated with study amendments as appropriate. However, it is not fully understood why an initial version 1.0 was not approved on 22 August 2016 and the rest of versions following the study amendments with impact on the SAP. In any case, the potential impact on results is expected to be limited.

There were 4 amendments to the original protocol. The first amendment changed part of the inclusion criteria, allowing the inclusion of patients with high volume disease and removing those with ECOG 2. The former is understood. However, the exclusion of patients with a poorer performance status is only understood with the aim of improving the size of benefits. No clinical arguments can be identified.

It is noted that the interim analyses for OS were changed: from 50% initially to 60% and then in the amendment 4, again to 50%, but modifying the second from 75% to 70%. According to the MAH, the basis for these changes was the knowledge of external data relating to this population and time of the primary analysis for rPFS.

There were protocol deviations in approximately 10% of the patients. However, they are not considered critical.

Regarding the baseline characteristics, the population seems to be evenly balanced, even though only 11% of the ITT population previously received chemotherapy despite the majority of the population recruited could be considered fit for receiving docetaxel (good ECOG and high volume disease).

The demographic characteristics at baseline outline a population with metastatic disease at initial diagnosis, Gleason score >7, older than 65 and with no or slight pain.

At randomisation most of the patients had had any decline in the PSA value (95.6% in the apalutamide arm and 80.6% in the placebo arm) with more than half of the patients reaching a reduction of 50% or more in the PSA value (93% vs. 58.8%, apalutamide and placebo, respectively). However, there were 64

(6%) patients (31 in the apalutamide arm and 33 in the placebo arm) without a reduction in PSA value at the time of randomisation that might be considered as potential castration resistant. Due to the small number of patients (6%) and the fact that they seem to be evenly balanced, the impact of this issue is deemed minor. The SmPC reflects that, although criteria for castration resistance were not determined at baseline, 94% of patients demonstrated a decrease in prostate specific antigen (PSA) from initiation of androgen deprivation therapy (ADT) to first dose of apalutamide or placebo (see SmPC section 5.1).

Efficacy data and additional analyses

The Independent Data Monitoring Committee (IDMC) reviewed data from the 23 November 2018 clinical cut-off date for TITAN and unanimously recommended to unblind the study and offer patients assigned to the placebo + ADT arm an option to crossover to receive apalutamide + ADT.

As specified in the statistical plan, the rPFS endpoint was tested first at the two-sided 0.005 level of significance. Since rPFS was statistically significant, the OS endpoint was tested at the overall 0.05 level of significance. The interim analysis for OS was conducted when 200 patients had died (48.8% of the 410 planned final events). According to interim plan the alpha boundary of 0.0101 (Wang-Tsiatis power boundary with a shape parameter of 0.2) was crossed: HR: 0.67 (95% CI: 0.51, 0.89; p=0.0053), and thus, OS was statistically significant. With regards to this effect estimation, it is noted that the calculated 95%CI were not corrected as planned. The Applicant provided the confidence intervals for the HR with the appropriate corrected confidence level according to the interim plan (i.e. 98.99%): HR: 0.67 (98.99% CI: 0.46, 0.97)

The OS sensitivity analyses carried out point out in the same direction (non-stratified log rank test; HR=0.68; 95%CI: 0.51, 0.90 and Multivariate analysis of OS adjusting for baseline prognostic factors HR=0.617; 95% CI: 0.46, 0.83). To assess the impact of the use of subsequent therapies on the treatment effect on the OS, a time-dependent analysis using Cox regression using inverse probability censoring weighting (IPCW) was conducted: HR=0.483(95% CI: 0.360, 0.647). In this last analysis, only potential impact of subsequent therapies was analysed. It should be kept in mind that this study was still blinded when data for the interim OS analysis was locked, and no patients from the placebo arm had crossed over to the apalutamide arm. When the IDMC recommended unblinding the study, 243 patients in the placebo group were offered the opportunity to receive apalutamide. As of 04 October 2019, 202 patients have crossed over to the apalutamide arm. The potential impact on OS of patients who continued treatment after radiographic progression, especially in patients randomised to the placebo arm, was not controlled in this analysis. Further sensitivity analyses (i)censoring patients who continued treatment in placebo arm, ii) patients who continued treatment in apalutamide arm and iii) patients who continued treatment in both arms were submitted (data not shown). As the results of these analyses were similar to the primary OS analysis, the impact on OS of patient who continued treatment after radiographic progression was considered limited.

Regarding the subsequent therapies, apart from the previous IPCW analysis, 92 (51.1%) patients in the apalutamide arm and 197 (72.7%) patients in the placebo arm received subsequent therapy for prostate cancer, which may include radiotherapy, surgery and/or systemic therapy (i.e., hormonal therapy, chemotherapy). Among patients who discontinued treatment and were still alive, the proportion of patients that received subsequent hormonal therapy or chemotherapy was roughly similar.

Most of the OS subgroups analysed support the ITT analysis. The treatment effect observed was generally consistent in the subgroups evaluated, including high volume disease (HR=0.68) and low volume disease (HR=0.67). Only in the prior docetaxel group there seems to be an apparent lack of benefit with the point estimate beyond unity. However, due to the very low number of events, this result should be interpreted

carefully. The applicant has tried to justify this discrepancy by the baseline characteristics, which were not balanced within this subgroup (PSA and ECOG).

While the statistical significance in OS was reached, the number of deaths was only <50% of the total planned events and more importantly, the median follow-up was only approximately 22 months in both groups. It is noted that the plan tried to detect an increase in the median OS from 44 in the control arm to 59 months in the apalutamide arm. However, due to the interim study termination a number of patients were censored (852, 81%), many of them in the first part of the curve. More importantly, the study has substantially less follow-up than planned.

Even considering the interim termination of the trial, the high amount and in particular the early distribution in time of the censored data was not fully understood. Description and discussion on the reasons for censoring were provided. The applicant justified that the last patient was consented on 29 June 2017, but the last patient was randomized on 25 July 2017 or 16 months before the clinical cut-off. There was only 1 subject in each arm that was at risk and censored prior to 15 months and 87 patients who were at risk and censored during month 15 to 18 (placebo=48; apalutamide=39), in addition there were only 13 placebo and 15 apalutamide patients who were lost to follow-up or withdrew from the study by month 18.

Overall, the available data for OS appear to be insufficiently mature. The applicant states that an updated OS analysis is planned when approximately 410 events have been observed which is expected to be available by June 2021. However, the significance of OS will not be re-tested in this analysis. It should also be considered that around 91% of patients randomised to the placebo arm had crossed over to apalutamide, which can make more difficult to establish the contribution of apalutamide on OS. Nevertheless, the MAH is recommended to submit the updated and final OS analyses from the Phase 3 randomized, placebo-controlled, double-blind study 56029127PCR3002 (TITAN). This is expected to be available in June 2021.

On analysing the results in rPFS, the improvement in rPFS was consistently shown in the sensitivity analyses (based on the central review data, where the date of progression is defined as the date of the scan showing >=2 new bone lesions compared to the nadir of bone lesions) and in the central review in approximately 60% of patients. Regarding the subgroup analyses, there is no indication of any discordant subgroup. However, a higher number of patients in the experimental arm discontinued treatment by cut-off date (39 [7.4%] vs. 11 [2.1%]). The main reason for discontinuation for those patients who did not have a radiographic progression event but had discontinued study treatment was an adverse event in both arms (45.5% in placebo vs 56.4% in apalutamide).

Overall, consistent improvement in rPFS was observed across patient subgroups including high- or low-volume disease, prior docetaxel use (yes or no), age (< 65, ≥65, or ≥75 years old), baseline PSA above median (yes or no), and number of bone lesions (≤10 or >10).

Results on the secondary endpoints were tested according to the hierarchical plan, showing only positive findings for the first one (time to cytotoxic chemotherapy) and therefore stopping the analysis for the others. Time to pain progression, time to chronic opioid use, time to skeletal-related events had a positive trend favouring the apalutamide arm (according to the nominal p values).

Regarding other efficacy endpoints, there was a longer delay in the time to PSA progression and in terms of PFS2 for those patients treated with apalutamide vs placebo. The antitumor activity according to RECIST criteria in visceral, soft tissue and lymph nodes was 72% in the apalutamide+ADT vs 64% in the placebo+ADT arm. Death from a prostate cancer-specific cause showed a positive trend in favour of apalutamide + ADT (HR=0.74; 95%CI 0.53, 1.03). The PRO analyses did not reveal differences between the two arms of the study.

Overall, the results from the study are considered clinically meaningful, both in patients with low and high volume disease, and in patients with presence or absence of metastases at diagnosis. Likewise, the results do not seem to be modified according to the dichotomy between high risk and low risk.

2.4.4. Conclusions on the clinical efficacy

The addition of apalutamide upon the ADT provides a clinically meaningful delay in the progression of the disease in patients with metastatic hormone-sensitive prostate cancer. Even though, there are uncertainties on the magnitude of the benefit in terms of OS, the results in general are considered clinically relevant.

2.5. Clinical safety

Introduction

The summary of clinical safety incorporates data from 2 randomized, multicenter, placebo-controlled, Phase 3 studies (TITAN: mCSPC population and SPARTAN: NM-CRPC population), where apalutamide 240 mg was added to ADT in men with prostate cancer. The integrated safety population includes 2,252 patients: 1,327 patients treated with apalutamide + ADT and 925 patients treated with placebo + ADT. The clinical cut-off date is 23 November 2018 for TITAN and 19 September 2017 for SPARTAN.

The integrated analysis only presents treatment-emergent adverse events (TEAEs), which are defined as adverse events that occurred or worsened in severity from the first dose of study drug until 30 days after the last dose of study drug for TITAN and 28 days after the of last dose of study drug for SPARTAN.

Adverse event severity and abnormal laboratory results were graded according to the National Cancer Institute's Common Toxicity Criteria (NCI CTCAE) Version 4.03. Thyroid stimulating hormone values at baseline, postbaseline, and change from baseline were summarized. These were presented separately from chemistry results as NCI CTCAE grading was not applied to TSH values. Liver function test data were summarized based on eDISH and Hy's Law criteria (FDA 2009). Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 was used for the classification of AEs. Treatment-related AEs were those judged by the investigator to be at least possibly related to the blinded study drug.

TEAE analyses were performed by subgroups of patients (age, race, geographic region, baseline ECOG performance status, and baseline PSA).

To adjust for the time on treatment, the event rate of AEs per 100 patient-years (P-Y) of exposure was also analysed.

Determination of ADRs was based on the review of data from a total of 1,051 patients: apalutamide 240 mg (524 patients) or placebo (527 patients) in TITAN. ADR determination was primarily based upon the TITAN study data; however, the SPARTAN data were also considered during the selection process.

Patient exposure

The demographic characteristics and baseline disease characteristics were balanced between the treatment arm and control arm in both studies.

Patients in TITAN (median age of 68 years with 23% of patients 75 years or older and median weight of 77 kg) were younger and weighed less than patients in SPARTAN (median age of 74 years with 48% of patients 75 years or older and median weight of 84 kg). The majority of patients in both studies were

white (68% in TITAN and 66% in SPARTAN). In TITAN, the majority of patients were from the Rest of World region (Argentina, Australia, Brazil, China, Israel, Japan, Korea, Mexico, Russia, Turkey), while in SPARTAN, the majority of patients were from North America or Europe.

The observed differences in disease characteristics between the studies reflect the different patient populations enrolled in TITAN (mCSPC) and SPARTAN (NMCRPC).

A history of cardiac disorders, diabetes, or hypertension was noted for 66% of patients in the apalutamide + ADT arm and 61% of patients in the placebo + ADT arm in TITAN (75% vs 76% in SPARTAN).

As of the cut-off dates, a lower proportion of patients in the apalutamide + ADT arm discontinued treatment as compared with the placebo + ADT arm (34% apalutamide vs 54% placebo in TITAN and 43% vs 76% in SPARTAN). In both studies, the higher rate of treatment discontinuation in the placebo + ADT arm was mainly due to progressive disease. Treatment discontinuation due to AEs was more common in the apalutamide + ADT arm as compared with the placebo + ADT arm, but occurred less frequently in TITAN (7.4% apalutamide vs 3.2% placebo) as compared with SPARTAN (11% vs 6.5%). Skin rash (grouped term) was the most common reason for treatment discontinuation in the apalutamide + ADT arm in both studies.

Table 36: Treatment Disposition; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated safety	527	524	398	803	925	1327
Subjects with treatment ongoing[a]	243 (46.1%)	347 (66.2%)	94 (23.6%)	457 (56.9%)	337 (36.4%)	804 (60.6%)
Subjects discontinued from treatment	284 (53.9%)	177 (33.8%)	304 (76.4%)	346 (43.1%)	588 (63.6%)	523 (39.4%)
Reason for termination						
Progressive Disease	227 (43.1%)	99 (18.9%)	229 (57.5%)	179 (22.3%)	456 (49.3%)	278 (20.9%)
Adverse Event	17 (3.2%)	39 (7.4%)	26 (6.5%)	91 (11.3%)	43 (4.6%)	130 (9.8%)
Withdrawal By Subject	23 (4.4%)	22 (4.2%)	41 (10.3%)	56 (7.0%)	64 (6.9%)	78 (5.9%)
Other	0	1 (0.2%)	4 (1.0%)	11 (1.4%)	4 (0.4%)	12 (0.9%)
Death	13 (2.5%)	8 (1.5%)	0	0	13 (1.4%)	8 (0.6%)
Noncompliance With Study Procedures	0	0	0	6 (0.7%)	0	6 (0.5%)
Physician Decision	3 (0.6%)	6 (1.1%)	0	0	3 (0.3%)	6 (0.5%)
Protocol Violation	1 (0.2%)	2 (0.4%)	3 (0.8%)	3 (0.4%)	4 (0.4%)	5 (0.4%)
Lost To Follow-Up	0	0	1 (0.3%)	0	1 (0.1%)	0

[a]Reflects the status on the data cut-off dates of the related studies.

[TSIDS01.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSIDS01.SAS] 13FEB2019, 13:32

In TITAN, the median duration of treatment was 20 months for the apalutamide + ADT arm and 18 months for the placebo + ADT arm. As of the clinical cut-off date for TITAN (23 November 2018), 66% of patients in the treatment arm were continuing in the study. In SPARTAN median treatment duration for the placebo+ADT arm was lower in TITAN (11 months vs 18 months), while for the apalutamide + ADT arm duration is similar.

Table 37: Summary of Exposure; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated safety	527	524	398	803	925	1327
Treatment Duration (months)						
N	527	524	398	803	925	1327
Mean (SD)	16.67 (7.946)	19.02 (7.788)	13.48 (9.130)	19.70 (10.704)	15.29 (8.617)	19.43 (9.660)
Median	18.30	20.47	11.48	20.17	15.47	20.34
Range	(0.1; 34.0)	(0.0; 34.2)	(0.1; 37.5)	(0.1; 46.1)	(0.1; 37.5)	(0.0; 46.1)

Modified from [TSIEX01.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSIEX01.SAS] 13FEB2019, 13:32

Table 38: Summary of Study Drug Compliance for Apalutamide or Placebo; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated safety	527	524	398	803	925	1327
Overall Treatment Compliance (%)[a]						
N	527	522	397	803	924	1325
≤75%	7 (1.3%)	24 (4.6%)	22 (5.5%)	69 (8.6%)	29 (3.1%)	93 (7.0%)
>75% - ≤80%	2 (0.4%)	12 (2.3%)	9 (2.3%)	29 (3.6%)	11 (1.2%)	41 (3.1%)
>80% - ≤85%	6 (1.1%)	7 (1.3%)	14 (3.5%)	57 (7.1%)	20 (2.2%)	64 (4.8%)
>85% - ≤90%	9 (1.7%)	16 (3.1%)	28 (7.0%)	114 (14.2%)	37 (4.0%)	130 (9.8%)
>90% - ≤95%	33 (6.3%)	34 (6.5%)	51 (12.8%)	161 (20.0%)	84 (9.1%)	195 (14.7%)
>95%	470 (89.2%)	429 (81.9%)	273 (68.6%)	373 (46.5%)	743 (80.3%)	802 (60.4%)

[a]The percent overall treatment compliance will be defined as the total dose in mg taken during the study divided by the expected total dose in mg, multiplied by 100. A subject's expected total dose will be calculated as the assigned dose per day multiplied by treatment duration. Each patient should be taking 4 tablets per day maximum while on the study.

[TSIEX05.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSIEX05.SAS] 13FEB2019, 13:32

Table 39: Summary of Dose Adjustment for Apalutamide or Placebo; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set:						
Integrated Safety	527	524	398	803	925	1327
Number of dose level reduction due to an AE						
0	516 (97.9%)	486 (92.7%)	385 (96.7%)	712 (88.7%)	901 (97.4%)	1198 (90.3%)
1(to 180mg)	7 (1.3%)	24 (4.6%)	4 (1.0%)	46 (5.7%)	11 (1.2%)	70 (5.3%)
2(to 120mg)	4 (0.8%)	14 (2.7%)	9 (2.3%)	45 (5.6%)	13 (1.4%)	59 (4.4%)
Reason for dose level reduction						
Adverse Event	11 (2.1%)	38 (7.3%)	13 (3.3%)	91 (11.3%)	24 (2.6%)	129 (9.7%)
Other	12 (2.3%)	17 (3.2%)	50 (12.6%)	82 (10.2%)	62 (6.7%)	99 (7.5%)
Number of dose interruption due to an AE						
0	463 (87.9%)	401 (76.5%)	318 (79.9%)	526 (65.5%)	781 (84.4%)	927 (69.9%)
1	51 (9.7%)	86 (16.4%)	52 (13.1%)	172 (21.4%)	103 (11.1%)	258 (19.4%)
2	9 (1.7%)	22 (4.2%)	22 (5.5%)	59 (7.3%)	31 (3.4%)	81 (6.1%)
3	3 (0.6%)	15 (2.9%)	4 (1.0%)	31 (3.9%)	7 (0.8%)	46 (3.5%)
4	1 (0.2%)	0	0	6 (0.7%)	1 (0.1%)	6 (0.5%)
5	0	0	2 (0.5%)	5 (0.6%)	2 (0.2%)	5 (0.4%)
6	0	0	0	2 (0.2%)	0	2 (0.2%)
7	0	0	0	2 (0.2%)	0	2 (0.2%)
Reason for dose interruption						
Adverse Event	64 (12.1%)	123 (23.5%)	80 (20.1%)	277 (34.5%)	144 (15.6%)	400 (30.1%)
Other	200 (38.0%)	180 (34.4%)	193 (48.5%)	354 (44.1%)	393 (42.5%)	534 (40.2%)

[TSIEX02.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSIEX02.SAS] 13FEB2019, 13:32

In TITAN, all patients received at least 1 prior treatment for prostate cancer and received hormone therapy. Most patients in TITAN were only exposed to a short course of ADT prior to entry (71% received prior ADT for 3 months or less prior to randomization). A lower proportion of patients in TITAN (16%) had prior surgery or radiotherapy as compared with SPARTAN (77%).

Table 40: Prior Prostate Cancer Therapy; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated safety	527	524	398	803	925	1327
Subjects with at least 1 prior prostate cancer therapy	527 (100.0%)	524 (100.0%)	398 (100.0%)	800 (99.6%)	925 (100.0%)	1324 (99.8%)
Prostatectomy or radiotherapy	67 (12.7%)	81 (15.5%)	276 (69.3%)	534 (66.5%)	343 (37.1%)	615 (46.3%)
Prostatectomy only	28 (5.3%)	27 (5.2%)	40 (10.1%)	77 (9.6%)	68 (7.4%)	104 (7.8%)
Radiotherapy only[a]	27 (5.1%)	34 (6.5%)	145 (36.4%)	258 (32.1%)	172 (18.6%)	292 (22.0%)
Both prostatectomy and radiotherapy	12 (2.3%)	20 (3.8%)	91 (22.9%)	199 (24.8%)	103 (11.1%)	219 (16.5%)
Hormonal therapy	527 (100.0%)	524 (100.0%)	397 (99.7%)	798 (99.4%)	924 (99.9%)	1322 (99.6%)
Orchiectomy	40 (7.6%)	33 (6.3%)	24 (6.0%)	47 (5.9%)	64 (6.9%)	80 (6.0%)
GnRHa	489 (92.8%)	495 (94.5%)	385 (96.7%)	777 (96.8%)	874 (94.5%)	1272 (95.9%)
1st generation anti-androgen	361 (68.5%)	352 (67.2%)	287 (72.1%)	589 (73.3%)	648 (70.1%)	941 (70.9%)
Other	0	0	9 (2.3%)	17 (2.1%)	9 (1.0%)	17 (1.3%)
Chemotherapy	55 (10.4%)	58 (11.1%)	7 (1.8%)	17 (2.1%)	62 (6.7%)	75 (5.7%)
Other	0	1 (0.2%)	32 (8.0%)	64 (8.0%)	32 (3.5%)	65 (4.9%)

[a]Radiotherapy applicable only to prostate region has been included.
Note: surgery only applicable to prostatectomy has been included.
[TSIDEM03.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSIDEM03.SAS] 13FEB2019, 13:31

Bone-sparing agents were taken by 17% of apalutamide-treated patients and 24% of placebo-treated patients in TITAN.

Adverse events

Almost all patients in TITAN and SPARTAN were reported to have at least 1 or more TEAE (>93% across all groups). Grade 3-4 TEAEs were reported for 42% of patients in the apalutamide + ADT arm and 41% of patients in the placebo + ADT arm in TITAN (47% vs 35% in SPARTAN and 45% vs 38% in the combined population).

Table 41: Overall Safety Profile; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated Safety	527	524	398	803	925	1327
Subjects with 1 or more:						
TEAEs[b]	509 (96.6%)	507 (96.8%)	373 (93.7%)	779 (97.0%)	882 (95.4%)	1286 (96.9%)
Related TEAEs[a]	219 (41.6%)	315 (60.1%)	216 (54.3%)	569 (70.9%)	435 (47.0%)	884 (66.6%)
Grade 3-4 TEAEs	215 (40.8%)	221 (42.2%)	141 (35.4%)	378 (47.1%)	356 (38.5%)	599 (45.1%)
Related TEAEs[a]	31 (5.9%)	66 (12.6%)	18 (4.5%)	115 (14.3%)	49 (5.3%)	181 (13.6%)
Serious TEAEs[b]	107 (20.3%)	104 (19.8%)	98 (24.6%)	216 (26.9%)	205 (22.2%)	320 (24.1%)
Related serious TEAEs	4 (0.8%)	10 (1.9%)	7 (1.8%)	34 (4.2%)	11 (1.2%)	44 (3.3%)
Grade 3-4 serious TEAEs	86 (16.3%)	84 (16.0%)	82 (20.6%)	164 (20.4%)	168 (18.2%)	248 (18.7%)
TEAEs leading to treatment discontinuation	28 (5.3%)	42 (8.0%)	31 (7.8%)	91 (11.3%)	59 (6.4%)	133 (10.0%)
Related TEAEs[a]	4 (0.8%)	17 (3.2%)	8 (2.0%)	60 (7.5%)	12 (1.3%)	77 (5.8%)
TEAEs leading to death	16 (3.0%)	10 (1.9%)	2 (0.5%)	13 (1.6%)	18 (1.9%)	23 (1.7%)
Related TEAEs[a]	0	0	0	1 (0.1%)	0	1 (0.1%)
All deaths on study[c]	23 (4.4%)	18 (3.4%)	2 (0.5%)	13 (1.6%)	25 (2.7%)	31 (2.3%)
Adverse event	16 (3.0%)	10 (1.9%)	2 (0.5%)	10 (1.2%)	18 (1.9%)	20 (1.5%)
Death due to prostate cancer	7 (1.3%)	8 (1.5%)	0	3 (0.4%)	7 (0.8%)	11 (0.8%)
Other	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for study 56021927PCR3002 are considered as on treatment death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0
[TSFAE01.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSFAE01.SAS] 14FEB2019, 10:14

In TITAN, the most frequently reported TEAEs (≥15% of patients in either arm) of skin rash (grouped term), fatigue, back pain, hypertension, and arthralgia were also frequently reported in the combined population. Hot flush and weight increased were frequently reported TEAEs in the TITAN study only. The majority of these events were Grade 1 or 2. These events seldom led to treatment discontinuation (≤1.5%) and were rarely considered to be SAEs (≤1.1%). With the exception of skin rash (grouped term), these events infrequently led to dose modifications.

Table 42: Number of Patients with Treatment-emergent Adverse Events with Frequency of at Least 5% in Any Group by System Organ Class and Preferred Term

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated Safety	527	524	398	803	925	1327
Subjects with 1 or more TEAEs	509 (96.6%)	507 (96.8%)	373 (93.7%)	779 (97.0%)	882 (95.4%)	1286 (96.9%)
System organ class						
Preferred term						
Gastrointestinal disorders	197 (37.4%)	195 (37.2%)	235 (59.0%)	479 (59.7%)	432 (46.7%)	674 (50.8%)
Diarrhoea	32 (6.1%)	49 (9.4%)	61 (15.3%)	167 (20.8%)	93 (10.1%)	216 (16.3%)
Nausea	41 (7.8%)	36 (6.9%)	63 (15.8%)	148 (18.4%)	104 (11.2%)	184 (13.9%)
Constipation	57 (10.8%)	47 (9.0%)	53 (13.3%)	90 (11.2%)	110 (11.9%)	137 (10.3%)
Abdominal pain	22 (4.2%)	12 (2.3%)	34 (8.5%)	69 (8.6%)	56 (6.1%)	81 (6.1%)
Dyspepsia	10 (1.9%)	11 (2.1%)	22 (5.5%)	59 (7.3%)	32 (3.5%)	70 (5.3%)
Vomiting	21 (4.0%)	18 (3.4%)	25 (6.3%)	46 (5.7%)	46 (5.0%)	64 (4.8%)
Abdominal pain upper	11 (2.1%)	17 (3.2%)	33 (8.3%)	44 (5.5%)	44 (4.8%)	61 (4.6%)
Abdominal discomfort	2 (0.4%)	2 (0.4%)	24 (6.0%)	38 (4.7%)	26 (2.8%)	40 (3.0%)
Musculoskeletal and connective tissue disorders	307 (58.3%)	287 (54.8%)	163 (41.0%)	383 (47.7%)	470 (50.8%)	670 (50.5%)
Arthralgia	78 (14.8%)	91 (17.4%)	33 (8.3%)	136 (16.9%)	111 (12.0%)	227 (17.1%)
Back pain	102 (19.4%)	91 (17.4%)	60 (15.1%)	106 (13.2%)	162 (17.5%)	197 (14.8%)
Pain in extremity	67 (12.7%)	64 (12.2%)	20 (5.0%)	77 (9.6%)	87 (9.4%)	141 (10.6%)
Musculoskeletal pain	41 (7.8%)	35 (6.7%)	16 (4.0%)	39 (4.9%)	57 (6.2%)	74 (5.6%)
Bone pain	53 (10.1%)	34 (6.5%)	5 (1.3%)	11 (1.4%)	58 (6.3%)	45 (3.4%)
General disorders and administration site conditions	199 (37.8%)	206 (39.3%)	159 (39.9%)	408 (50.8%)	358 (38.7%)	614 (46.3%)
Fatigue	88 (16.7%)	103 (19.7%)	85 (21.4%)	245 (30.5%)	173 (18.7%)	348 (26.2%)
Asthenia	44 (8.3%)	37 (7.1%)	33 (8.3%)	94 (11.7%)	77 (8.3%)	131 (9.9%)
Oedema peripheral	40 (7.6%)	31 (5.9%)	29 (7.3%)	72 (9.0%)	69 (7.5%)	103 (7.8%)
Infections and infestations	191 (36.2%)	182 (34.7%)	146 (36.7%)	351 (43.7%)	337 (36.4%)	533 (40.2%)
Viral upper respiratory tract infection	48 (9.1%)	36 (6.9%)	26 (6.5%)	83 (10.3%)	74 (8.0%)	119 (9.0%)
Urinary tract infection	22 (4.2%)	27 (5.2%)	39 (9.8%)	67 (8.3%)	61 (6.6%)	94 (7.1%)
Upper respiratory tract infection	28 (5.3%)	34 (6.5%)	21 (5.3%)	46 (5.7%)	49 (5.3%)	80 (6.0%)
Skin and subcutaneous tissue disorders	93 (17.6%)	207 (39.5%)	67 (16.8%)	322 (40.1%)	160 (17.3%)	529 (39.9%)
Rash	19 (3.6%)	80 (15.3%)	13 (3.3%)	89 (11.1%)	32 (3.5%)	169 (12.7%)
Pruritus	24 (4.6%)	56 (10.7%)	6 (1.5%)	51 (6.4%)	30 (3.2%)	107 (8.1%)
Rash maculo-papular	5 (0.9%)	17 (3.2%)	2 (0.5%)	43 (5.4%)	7 (0.8%)	60 (4.5%)
Rash generalised	5 (0.9%)	34 (6.5%)	1 (0.3%)	19 (2.4%)	6 (0.6%)	53 (4.0%)
Vascular disorders	161 (30.6%)	195 (37.2%)	119 (29.9%)	330 (41.1%)	280 (30.3%)	525 (39.6%)
Hypertension	82 (15.6%)	93 (17.7%)	81 (20.4%)	204 (25.4%)	163 (17.6%)	297 (22.4%)
Hot flush	86 (16.3%)	119 (22.7%)	34 (8.5%)	116 (14.4%)	120 (13.0%)	235 (17.7%)
Metabolism and nutrition disorders	111 (21.1%)	143 (27.3%)	86 (21.6%)	282 (35.1%)	197 (21.3%)	425 (32.0%)
Decreased appetite	27 (5.1%)	30 (5.7%)	35 (8.8%)	105 (13.1%)	62 (6.7%)	135 (10.2%)
Hypercholesterolaemia	4 (0.8%)	24 (4.6%)	6 (1.5%)	51 (6.4%)	10 (1.1%)	75 (5.7%)
Hyperkalaemia	27 (5.1%)	39 (7.4%)	8 (2.0%)	34 (4.2%)	35 (3.8%)	73 (5.5%)
Hyperglycaemia	9 (1.7%)	13 (2.5%)	16 (4.0%)	47 (5.9%)	25 (2.7%)	60 (4.5%)
Nervous system disorders	128 (24.3%)	130 (24.8%)	91 (22.9%)	295 (36.7%)	219 (23.7%)	425 (32.0%)
Headache	29 (5.5%)	35 (6.7%)	25 (6.3%)	78 (9.7%)	54 (5.8%)	113 (8.5%)
Dizziness	32 (6.1%)	15 (2.9%)	27 (6.8%)	75 (9.3%)	59 (6.4%)	90 (6.8%)
Dysgeusia	3 (0.6%)	17 (3.2%)	6 (1.5%)	57 (7.1%)	9 (1.0%)	74 (5.6%)
Investigations	187 (35.5%)	141 (26.9%)	64 (16.1%)	236 (29.4%)	251 (27.1%)	377 (28.4%)
Weight decreased	27 (5.1%)	34 (6.5%)	25 (6.3%)	134 (16.7%)	52 (5.6%)	168 (12.7%)
Weight increased	89 (16.9%)	54 (10.3%)	9 (2.3%)	25 (3.1%)	98 (10.6%)	79 (6.0%)
Alanine aminotransferase increased	40 (7.6%)	24 (4.6%)	7 (1.8%)	14 (1.7%)	47 (5.1%)	38 (2.9%)
Aspartate aminotransferase increased	42 (8.0%)	17 (3.2%)	6 (1.5%)	15 (1.9%)	48 (5.2%)	32 (2.4%)
Blood alkaline phosphatase increased	28 (5.3%)	16 (3.1%)	2 (0.5%)	8 (1.0%)	30 (3.2%)	24 (1.8%)
Renal and urinary disorders	118 (22.4%)	116 (22.1%)	150 (37.7%)	253 (31.5%)	268 (29.0%)	369 (27.8%)
Haematuria	16 (3.0%)	21 (4.0%)	43 (10.8%)	69 (8.6%)	59 (6.4%)	90 (6.8%)
Dysuria	28 (5.3%)	32 (6.1%)	24 (6.0%)	42 (5.2%)	52 (5.6%)	74 (5.6%)
Pollakiuria	19 (3.6%)	18 (3.4%)	34 (8.5%)	47 (5.9%)	53 (5.7%)	65 (4.9%)
Urinary incontinence	6 (1.1%)	11 (2.1%)	15 (3.8%)	43 (5.4%)	21 (2.3%)	54 (4.1%)
Nocturia	13 (2.5%)	12 (2.3%)	30 (7.5%)	39 (4.9%)	43 (4.6%)	51 (3.8%)
Urinary retention	19 (3.6%)	13 (2.5%)	36 (9.0%)	35 (4.4%)	55 (5.9%)	48 (3.6%)
Hydronephrosis	10 (1.9%)	5 (1.0%)	22 (5.5%)	18 (2.2%)	32 (3.5%)	23 (1.7%)
Injury, poisoning and procedural complications	81 (15.4%)	88 (16.8%)	74 (18.6%)	245 (30.5%)	155 (16.8%)	333 (25.1%)
Fall	37 (7.0%)	39 (7.4%)	37 (9.3%)	135 (16.8%)	74 (8.0%)	174 (13.1%)
Respiratory, thoracic and mediastinal disorders	91 (17.3%)	98 (18.7%)	83 (20.9%)	227 (28.3%)	174 (18.8%)	325 (24.5%)
Cough	30 (5.7%)	32 (6.1%)	28 (7.0%)	62 (7.7%)	58 (6.3%)	94 (7.1%)
Dyspnoea	16 (3.0%)	13 (2.5%)	18 (4.5%)	66 (8.2%)	34 (3.7%)	79 (6.0%)
Psychiatric disorders	48 (9.1%)	56 (10.7%)	53 (13.3%)	146 (18.2%)	101 (10.9%)	202 (15.2%)
Insomnia	31 (5.9%)	24 (4.6%)	21 (5.3%)	55 (6.8%)	52 (5.6%)	79 (6.0%)
Blood and lymphatic system disorders	100 (19.0%)	84 (16.0%)	33 (8.3%)	92 (11.5%)	133 (14.4%)	176 (13.3%)
Anaemia	71 (13.5%)	48 (9.2%)	16 (4.0%)	55 (6.8%)	87 (9.4%)	103 (7.8%)
Endocrine disorders	11 (2.1%)	22 (4.2%)	8 (2.0%)	57 (7.1%)	19 (2.1%)	79 (6.0%)
Hypothyroidism	3 (0.6%)	19 (3.6%)	5 (1.3%)	50 (6.2%)	8 (0.9%)	69 (5.2%)

Key: TEAE = treatment-emergent adverse event
Note: Grade 5 events are not included.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 20.0

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Table 43: Characteristics of Most Frequently Reported Adverse Events in TITAN

Adverse Event Characteristic	Placebo + ADT	Apalutamide + ADT
Skin Rash (Grouped Term)		
Incidence	45 (8.5%)	142 (27%)
Severity	Grade 3: 3 (0.6%) Grade 4: 0	Grade 3: 33 (6.3%) Grade 4: 0
Serious	0	0.4%
Leading to Treatment Discontinuation	0.2%	1.5%
Leading to Dose Modification	Interruption:0.8% Reduction: 0.6%	Interruption:7.4% Reduction: 4.8%
Hot Flush		
Incidence	86 (16%)	119 (23%)
Severity	Grade 3: 0 Grade 4: 0	Grade 3: 0 Grade 4: 0
Serious	0	0
Leading to Treatment Discontinuation	0	0.2%
Leading to Dose Modification	Interruption:0.2% Reduction: 0	Interruption:0.2% Reduction: 0.2%
Fatigue		
Incidence	88 (17%)	103 (20%)
Severity	Grade 3: 6 (1.1%) Grade 4: 0	Grade 3: 8 (1.5%) Grade 4: 0
Serious	0.4%	0
Leading to Treatment Discontinuation	0	0.8%
Leading to Dose Modification	Interruption:0.4% Reduction: 0	Interruption:1.1% Reduction: 0.4%
Back Pain		
Incidence	102 (19%)	91 (17%)
Severity	Grade 3: 13 (2.5%) Grade 4: 1 (0.2%)	Grade 3: 12 (2.3%) Grade 4: 0
Serious	1.1%	0.4%
Leading to Treatment Discontinuation	0	0
Leading to Dose Modification	Interruption: 0 Reduction: 0	Interruption:0.6% Reduction: 0
Hypertension		
Incidence	82 (16%)	93 (18%)
Severity	Grade 3: 48 (9.1%) Grade 4: 0	Grade 3: 44 (8.4%) Grade 4: 0
Serious	0	0.4%
Leading to Treatment Discontinuation	0	0
Leading to Dose Modification	Interruption:1.1% Reduction: 0.2%	Interruption:1.1% Reduction: 0.2%
Arthralgia		
Incidence	78 (15%)	91 (17%)
Severity	Grade 3: 5 (0.9%) Grade 4: 0	Grade 3: 2 (0.4%) Grade 4: 0
Serious	0	0.2%
Leading to Treatment Discontinuation	0	0
Leading to Dose Modification	Interruption: 0.2% Reduction: 0	Interruption:0.4% Reduction: 0
Weight increased		
Incidence	89 (17%)	54 (10%)
Severity	Grade 3: 10 (1.9%) Grade 4: 0	Grade 3: 6 (1.1%) Grade 4: 0
Serious	0	0
Leading to Treatment Discontinuation	0	0
Leading to Dose Modification	Interruption: 0.2% Reduction: 0	Interruption:0 Reduction:0

Source: Mod5.3.5.3/ISS/TableTSFAE02, Mod5.3.5.3/ISS/TSFAE04, Mod5.3.5.3/ISS/TSFAE06, Mod5.3.5.3/ISS/TSFAE07, Mod5.3.5.3/ISS/TSFAE08, Mod5.3.5.3/ISS/TSFAE17, Mod5.3.5.3/ISS/TSFAE19, Mod5.3.5.3/ISS/TSFAE19a, Mod5.3.5.3/ISS/TSFAE19b, Mod5.3.5.3/ISS/TSFAE19c, Mod5.3.5.1/PCR3002/AttTSFAE27R, Mod5.3.5.1/PCR3002/AttTSFAE27I

Table 44: Characteristics of Most Frequently Reported Adverse Events in SPARTAN

Adverse Event Characteristic	Placebo + ADT	Apalutamide + ADT
Fatigue		
Incidence	85 (21%)	245 (31%)
Severity	Grade 3: 1 (0.3%) Grade 4: 0	Grade 3: 7 (0.9%) Grade 4: 0
Serious	0	0
Leading to Treatment Discontinuation	0.3%	1.1%
Leading to Dose Modification	Interruption: 0.5% Reduction: 0	Interruption: 2.2% Reduction: 1.7%
Hypertension		
Incidence	81 (20%)	204 (25%)
Severity	Grade 3: 47 (12%) Grade 4: 0	Grade 3: 116 (14%) Grade 4: 0
Serious	0.8%	0.1%
Leading to Treatment Discontinuation	0.3%	0.1%
Leading to Dose Modification	Interruption: 0.8% Reduction: 0	Interruption: 1.2% Reduction: 0.2%
Skin Rash (Grouped Term)		
Incidence	22 (5.5%)	195 (24%)
Severity	Grade 3: 1 (0.3%) Grade 4: 0	Grade 3: 42 (5.2%) Grade 4: 0
Serious	0	0.2%
Leading to Treatment Discontinuation	0	2.4%
Leading to Dose Modification	Interruption: 1.3% Reduction: 0.3%	Interruption: 6.7% Reduction: 2.7%
Diarrhea		
Incidence	61 (15%)	167 (21%)
Severity	Grade 3: 2 (0.5%) Grade 4: 0	Grade 3: 8 (1.0%) Grade 4: 0
Serious	0.3%	0.6%
Leading to Treatment Discontinuation	0.3%	0.1%
Leading to Dose Modification	Interruption: 1.3% Reduction: 0	Interruption: 2.5% Reduction: 0.5%
Nausea		
Incidence	63 (16%)	148 (18%)
Severity	Grade 3: 0 Grade 4: 0	Grade 3: 0 Grade 4: 0
Serious	0	0.1%
Leading to Treatment Discontinuation	0	0.4%
Leading to Dose Modification	Interruption: 1.0% Reduction: 0.3%	Interruption:1.6% Reduction: 0.4%
Arthralgia		
Incidence	33 (8.3%)	136 (17%)
Severity	Grade 3: 0 Grade 4: 0	Grade 3: 1 (0.1%) Grade 4: 0
Serious	0	0.1%
Leading to Treatment Discontinuation	0	0
Leading to Dose Modification	Interruption: 0 Reduction: 0	Interruption: 0.4% Reduction: 0
Fall		
Incidence	37 (9.3%)	135 (17%)
Severity	Grade 3: 3 (0.8%) Grade 4: 0	Grade 3: 16 (2.0%) Grade 4: 0
Serious	0.3%	0.9%
Leading to Treatment Discontinuation	0	0.1%
Leading to Dose Modification	Interruption:0 Reduction: 0	Interruption:0.5% Reduction: 0
Weight Decreased		
Incidence	25 (6.3%)	134 (17%)
Severity	Grade 3: 1 (0.3%) Grade 4: 0	Grade 3: 10 (1.2%) Grade 4: 0
Serious	0	0.2%
Leading to Treatment Discontinuation	0	0.2%
Leading to Dose Modification	Interruption: 0 Reduction: 0	Interruption: 0.2% Reduction: 0.1%
Back Pain		
Incidence	60 (15%)	106 (13%)
Severity	Grade 3: 6 (1.5%) Grade 4: 0	Grade 3: 6 (0.7%) Grade 4: 0
Serious	0.3%	0.2%
Leading to Treatment Discontinuation	0	0
Leading to Dose Modification	Interruption: 0 Reduction: 0	Interruption: 0.5% Reduction: 0

Source: Mod5.3.5.3/ISS/TableTSFAE02, Mod5.3.5.3/ISS/TSFAE04, Mod5.3.5.3/ISS/TSFAE06, Mod5.3.5.3/ISS/TSFAE07, Mod5.3.5.3/ISS/TSFAE08, Mod5.3.5.3/ISS/TSFAE17, Mod5.3.5.3/ISS/TSFAE19, Mod5.3.5.3/ISS/TSFAE19a, Mod5.3.5.3/ISS/TSFAE19b, Mod5.3.5.3/ISS/TSFAE19c, Mod5.3.5.1/PCR3002/AttTSFAE27R, ARN-509-003SafetyUpdate2017/AttTSFAE27I, ARN-509-003SafetyUpdate2017/AttTSFAE27R

In TITAN, the most frequently reported Grade 3 or 4 TEAEs (≥3% of patients in either arm) were hypertension, skin rash (grouped term) and anemia. Hypertension and skin rash were the most frequently reported Grade 3 or 4 TEAEs (≥3% of patients in either arm).

Adverse events of special interest

Adverse events of special interest for apalutamide are skin rash, fall, fracture, seizure and hypothyroidism. There was a higher incidence of adverse events of special interest reported in the apalutamide +ADT arm as compared with the placebo + ADT arm in TITAN (38% vs 17%), SPARTAN (44% vs 19%) and the combined population (42% apalutamide vs 18% placebo).

Table 45: Treatment-emergent Adverse Events of Special Interest by Preferred Term; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set:Integrated Safety	527	524	398	803	925	1327
Subjects with 1 or more TEAEs of special interest	88 (16.7%)	199 (38.0%)	74 (18.6%)	355 (44.2%)	162 (17.5%)	554 (41.7%)
Special interest category Preferred term						
Skin rash	45 (8.5%)	142 (27.1%)	22 (5.5%)	195 (24.3%)	67 (7.2%)	337 (25.4%)
Rash	19 (3.6%)	80 (15.3%)	13 (3.3%)	89 (11.1%)	32 (3.5%)	169 (12.7%)
Rash maculo-papular	5 (0.9%)	17 (3.2%)	2 (0.5%)	43 (5.4%)	7 (0.8%)	60 (4.5%)
Rash generalised	5 (0.9%)	34 (6.5%)	1 (0.3%)	19 (2.4%)	6 (0.6%)	53 (4.0%)
Urticaria	4 (0.8%)	4 (0.8%)	1 (0.3%)	17 (2.1%)	5 (0.5%)	21 (1.6%)
Conjunctivitis	5 (0.9%)	10 (1.9%)	0	7 (0.9%)	5 (0.5%)	17 (1.3%)
Rash pruritic	3 (0.6%)	6 (1.1%)	2 (0.5%)	11 (1.4%)	5 (0.5%)	17 (1.3%)
Rash macular	0	1 (0.2%)	1 (0.3%)	10 (1.2%)	1 (0.1%)	11 (0.8%)
Stomatitis	4 (0.8%)	7 (1.3%)	1 (0.3%)	3 (0.4%)	5 (0.5%)	10 (0.8%)
Rash papular	1 (0.2%)	4 (0.8%)	1 (0.3%)	5 (0.6%)	2 (0.2%)	9 (0.7%)
Skin exfoliation	1 (0.2%)	5 (1.0%)	0	4 (0.5%)	1 (0.1%)	9 (0.7%)
Erythema multiforme	0	2 (0.4%)	0	4 (0.5%)	0	6 (0.5%)
Mouth ulceration	0	3 (0.6%)	1 (0.3%)	2 (0.2%)	1 (0.1%)	5 (0.4%)
Rash erythematous	0	1 (0.2%)	0	4 (0.5%)	0	5 (0.4%)
Blister	0	3 (0.6%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	4 (0.3%)
Drug eruption	0	2 (0.4%)	1 (0.3%)	2 (0.2%)	1 (0.1%)	4 (0.3%)
Genital rash	0	1 (0.2%)	0	3 (0.4%)	0	4 (0.3%)
Rash pustular	0	1 (0.2%)	0	2 (0.2%)	0	3 (0.2%)
Exfoliative rash	0	2 (0.4%)	0	0	0	2 (0.2%)
Papule	1 (0.2%)	1 (0.2%)	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Toxic skin eruption	0	2 (0.4%)	0	0	0	2 (0.2%)
Butterfly rash	0	1 (0.2%)	0	0	0	1 (0.1%)
Dermatitis exfoliative	0	1 (0.2%)	0	0	0	1 (0.1%)
Genital ulceration	0	0	0	1 (0.1%)	0	1 (0.1%)
Pemphigoid	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Skin erosion	0	0	0	1 (0.1%)	0	1 (0.1%)
Skin reaction	1 (0.2%)	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)
Systemic lupus erythematosus rash	0	1 (0.2%)	0	0	0	1 (0.1%)
Rash follicular	1 (0.2%)	0	0	0	1 (0.1%)	0
Rash vesicular	0	0	1 (0.3%)	0	1 (0.1%)	0

Fall	37 (7.0%)	39 (7.4%)	37 (9.3%)	135 (16.8%)	74 (8.0%)	174 (13.1%)
Fall	37 (7.0%)	39 (7.4%)	37 (9.3%)	135 (16.8%)	74 (8.0%)	174 (13.1%)
Fracture	24 (4.6%)	33 (6.3%)	29 (7.3%)	106 (13.2%)	53 (5.7%)	139 (10.5%)
Rib fracture	12 (2.3%)	12 (2.3%)	17 (4.3%)	39 (4.9%)	29 (3.1%)	51 (3.8%)
Spinal compression fracture	2 (0.4%)	5 (1.0%)	1 (0.3%)	8 (1.0%)	3 (0.3%)	13 (1.0%)
Lumbar vertebral fracture	0	0	0	10 (1.2%)	0	10 (0.8%)
Foot fracture	1 (0.2%)	2 (0.4%)	0	7 (0.9%)	1 (0.1%)	9 (0.7%)
Hip fracture	0	2 (0.4%)	0	5 (0.6%)	0	7 (0.5%)
Spinal fracture	0	1 (0.2%)	1 (0.3%)	6 (0.7%)	1 (0.1%)	7 (0.5%)
Upper limb fracture	0	3 (0.6%)	1 (0.3%)	4 (0.5%)	1 (0.1%)	7 (0.5%)
Thoracic vertebral fracture	0	2 (0.4%)	0	4 (0.5%)	0	6 (0.5%)
Femur fracture	0	2 (0.4%)	1 (0.3%)	3 (0.4%)	1 (0.1%)	5 (0.4%)
Humerus fracture	0	0	0	5 (0.6%)	0	5 (0.4%)
Wrist fracture	0	2 (0.4%)	0	3 (0.4%)	0	5 (0.4%)
Hand fracture	1 (0.2%)	1 (0.2%)	0	3 (0.4%)	1 (0.1%)	4 (0.3%)
Acetabulum fracture	0	1 (0.2%)	0	2 (0.2%)	0	3 (0.2%)
Fractured sacrum	0	0	0	3 (0.4%)	0	3 (0.2%)
Lower limb fracture	1 (0.2%)	1 (0.2%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Pubis fracture	0	0	1 (0.3%)	3 (0.4%)	1 (0.1%)	3 (0.2%)
Traumatic fracture	0	2 (0.4%)	0	1 (0.1%)	0	3 (0.2%)
Ankle fracture	2 (0.4%)	0	0	2 (0.2%)	2 (0.2%)	2 (0.2%)
Compression fracture	0	0	0	2 (0.2%)	0	2 (0.2%)
Costal cartilage fracture	0	0	1 (0.3%)	2 (0.2%)	1 (0.1%)	2 (0.2%)
Facial bones fracture	0	0	3 (0.8%)	2 (0.2%)	3 (0.3%)	2 (0.2%)
Osteoporotic fracture	0	0	2 (0.5%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Radius fracture	3 (0.6%)	1 (0.2%)	0	1 (0.1%)	3 (0.3%)	2 (0.2%)
Sternal fracture	0	1 (0.2%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Avulsion fracture	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Clavicle fracture	0	1 (0.2%)	0	0	0	1 (0.1%)
Fibula fracture	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Forearm fracture	0	1 (0.2%)	0	0	0	1 (0.1%)
Fracture	0	1 (0.2%)	0	0	0	1 (0.1%)
Fracture pain	0	1 (0.2%)	0	0	0	1 (0.1%)
Fractured coccyx	0	0	0	1 (0.1%)	0	1 (0.1%)
Fractured ischium	0	1 (0.2%)	0	0	0	1 (0.1%)
Patella fracture	0	1 (0.2%)	0	0	0	1 (0.1%)
Pelvic fracture	0	0	0	1 (0.1%)	0	1 (0.1%)
Stress fracture	0	0	0	1 (0.1%)	0	1 (0.1%)
Ulna fracture	0	1 (0.2%)	0	0	0	1 (0.1%)
Cervical vertebral fracture	0	0	1 (0.3%)	0	1 (0.1%)	0
Femoral neck fracture	1 (0.2%)	0	1 (0.3%)	0	2 (0.2%)	0
Skull fracture	1 (0.2%)	0	0	0	1 (0.1%)	0
Tibia fracture	1 (0.2%)	0	1 (0.3%)	0	2 (0.2%)	0
Hypothyroidism	6 (1.1%)	34 (6.5%)	8 (2.0%)	69 (8.6%)	14 (1.5%)	103 (7.8%)
Hypothyroidism	3 (0.6%)	19 (3.6%)	5 (1.3%)	50 (6.2%)	8 (0.9%)	69 (5.2%)
Blood thyroid stimulating hormone increased	2 (0.4%)	15 (2.9%)	2 (0.5%)	24 (3.0%)	4 (0.4%)	39 (2.9%)
Thyroxine decreased	0	0	1 (0.3%)	4 (0.5%)	1 (0.1%)	4 (0.3%)
Autoimmune thyroiditis	1 (0.2%)	1 (0.2%)	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Thyroxine free decreased	0	0	0	1 (0.1%)	0	1 (0.1%)
Tri-iodothyronine decreased	0	0	0	1 (0.1%)	0	1 (0.1%)
Seizure	2 (0.4%)	3 (0.6%)	0	2 (0.2%)	2 (0.2%)	5 (0.4%)
Seizure	1 (0.2%)	3 (0.6%)	0	2 (0.2%)	1 (0.1%)	5 (0.4%)
Tongue biting	1 (0.2%)	0	0	0	1 (0.1%)	0

Key: TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 20.0
[TSFAE19.RTF] [JNJ-56021927\Z_SCS\DBR_PCR3002ISS\RE_PCR3002ISS\PROD\TSFAE19.SAS] 14FEB2019, 10:22

Skin rash

Skin rash (as a grouped term) was more common for patients in the apalutamide + ADT arm as compared with patients in the placebo + ADT arm in TITAN (27% vs 8.5%), SPARTAN (24% vs 5.5%) and the combined population (25% apalutamide vs 7.2% placebo). The majority of the events were Grade 1 or 2. Dose modifications due to skin rash were more common in the treatment arm as compared with the control arm. Adverse events of skin rash seldom led to treatment discontinuation. In the apalutamide + ADT arm, there were 2 SAEs of skin rash in TITAN (drug eruption and generalized rash) and 2 SAEs of skin rash in SPARTAN (erythema multiforme and mouth ulceration). There were no reported events of toxic epidermal necrolysis or Stevens-Johnson syndrome in either study.

In both studies, events of rash usually occurred within the first few months of treatment and were actively managed with steroids or antihistamines; the majority of cases resolved.

In the combined dataset, adverse reactions of skin rash were reported for 26% of patients treated with apalutamide. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with apalutamide treatment in 6% of patients. The median days to onset of skin rash was 83 days.

Seventy-eight percent of patients had resolution of rash with a median of 78 days to resolution. Medicinal products utilised included topical corticosteroids, oral anti-histamines, and 19% of patients received systemic corticosteroids. Among patients with skin rash, dose interruption occurred in 28% and dose reduction occurred in 14%. Skin rash recurred in 59% of patients who had dose interruption. Skin rash led to apalutamide treatment discontinuation in 7% of patients who experienced skin rash.

Fall

Fall was reported in 7.4% of patients in the apalutamide + ADT arm and 7.0% of patients in the placebo + ADT arm in TITAN (17% vs 9.3% in SPARTAN and 13% vs 8.0% in the combined population). The majority of the events of Fall were Grade 1 or 2. Grade 3 events were reported in 0.8% in the placebo and apalutamide arm. There were no Grade 4 events. Events of Fall seldom led to treatment discontinuation or dose modification and were rarely considered to be SAEs.

For patients with an event fall, there was not a higher incidence of events of cognitive deficits (including memory impairment, amnesia, disturbance in attention and cognitive disorder) reported in the treatment arm as compared with the control arm, within one year before or after the event of fall. In TITAN, 2.6% of patients in the apalutamide + ADT arm and 2.7% of patients in the placebo + ADT arm who reported an event fall also reported an event in the grouped term of cognitive deficit within one year (3.7% vs 5.4% in SPARTAN and 3.4% vs 4.1% in the combined population).

Fracture

A potential mechanism for increased fracture risk is the enhanced blockade of the AR with apalutamide treatment. As such, bone-sparing agents were permitted concomitant medications in both studies. Bone-sparing agents were taken by 17% of apalutamide-treated patients and 24% of placebo-treated patients in TITAN (12% of patients in both arms of SPARTAN).

Fracture (grouped term) was reported in 6.3% of patients in the apalutamide + ADT arm and 4.6% of patients in the placebo + ADT arm in TITAN (13% vs 7.3% in SPARTAN and 10 % vs 5.7% in the combined population).

Rib fracture was the most commonly reported event in the grouped term of fracture, occurring in 2.3% of apalutamide-treated patients and 2.3% of placebo-treated patients in TITAN (4.3% vs 4.9% in SPARTAN and 3.8 % vs 3.1% in the combined population).

The majority of the events of fracture were Grade 1 or 2. Grade 3 and Grade 4 of fracture were reported in 1.1% and 0.2% of patients in the apalutamide + ADT arm vs 0.8% and 0 of patients in the placebo + ADT arm in TITAN (2.9% and 0 vs 1.0% and 0 in SPARTAN). SAEs of fracture were reported in 1.5% of patients in the apalutamide + ADT arm vs 0.9% of patients in the placebo + ADT arm in TITAN (3.5% vs 1.0% in SPARTAN). TEAEs of fracture seldom led to treatment discontinuation or dose modification.

A prior fall preceding fracture was common. Nearly half of patients with fracture had reported a fall in the 7 days prior to the fracture (52% apalutamide vs 42% placebo in TITAN and 41% vs 45% in SPARTAN).

The metastatic population in TITAN was younger, had a shorter duration of ADT exposure than the non-metastatic population in SPARTAN.

Seizure

Seizure (grouped term) was reported for 3 patients (0.6%) *[Grade 2 seizure in a subject with brain metastases, Grade 3 seizure in a subject with dehydration and fever, and Grade 2 seizure in a subject with brain metastases and intracranial hemorrhage]* in the apalutamide + ADT arm and 2 patients (0.4%) *[Grade 2 seizure in a subject with a metastatic brain lesion and Grade 1 tongue biting due to nerve compression from a metastatic lesion]* in the placebo + ADT arm. Two patients (0.2%) *[Grade 1 seizure in a subject with a history of febrile*

seizure, and Grade 2 seizure considered to be a result of a contusion from a fall in a subject with a history of Parkinson's disease and multiple falls] vs 0% in SPARTAN (0.4% vs 0.2% in the combined population).

In the apalutamide + ADT arm, 2 patients discontinued treatment due to seizure, and the third subject interrupted treatment due to seizure (and then discontinued treatment due to disease progression). For the patients in the apalutamide + ADT arm, the event of seizure occurred from 159 to 650 days after the start of study drug.

Hypothyroidism

Hypothyroidism (as a grouped term) was more common in patients in the apalutamide + ADT arm as compared with patients in the placebo + ADT arm in TITAN (6.5% vs 1.1%), SPARTAN (8.6% vs 2.0%) and in the combined population (7.8% vs 1.5%).

Hypothyroidism did not lead to treatment discontinuation or dose modification and was not reported as an SAE in the TITAN study or in any placebo-treated patients in SPARTAN. Hypothyroidism led to dose reduction, treatment discontinuation, and was classified as an SAE in 0.1% of apalutamide-treated patients in SPARTAN. The change from baseline in TSH was greater in patients in the apalutamide + ADT arm as compared with patients in the placebo + ADT arm in both TITAN and SPARTAN. There were no Grade 3-4 events in TITAN and SPARTAN.

In the combined population, hypothyroidism was reported for 8% of patients treated with apalutamide and 2% of patients treated with placebo based on assessments of thyroid stimulating hormone (TSH) every 4 months. Hypothyroidism occurred in 30% of patients already receiving thyroid replacement therapy in the apalutamide arm and in 3% of patients in the placebo arm. In patients not receiving thyroid replacement therapy, hypothyroidism occurred in 7% of patients treated with apalutamide and in 2% of patients treated with placebo.

Cardiac Disorders

During treatment, hypertension was a commonly reported TEAE, and hypertriglyceridemia was a commonly reported Grade 3 or 4 laboratory abnormality in both studies.

The overall rate of Cardiac Disorders was higher in the apalutamide + ADT arm as compared with the placebo + ADT arm in TITAN (8.8% vs 5.9%), SPARTAN (13% vs 9.5%) and the combined population (11% apalutamide vs 7.5% placebo).

Table 46: Number of subjects with treatment-emergent cardiac disorders by sub-category and preferred term; integrated safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated Safety	527	524	398	803	925	1327
Subjects with 1 or more Subjects with 1 or more treatment-emergent Cardiac Disorders	31 (5.9%)	46 (8.8%)	38 (9.5%)	103 (12.8%)	69 (7.5%)	149 (11.2%)
Category						
Subcategory						
Preferred term						
Cardiac Disorders	31 (5.9%)	46 (8.8%)	38 (9.5%)	103 (12.8%)	69 (7.5%)	149 (11.2%)
Arrhythmia	17 (3.2%)	21 (4.0%)	26 (6.5%)	70 (8.7%)	43 (4.6%)	91 (6.9%)
Atrial fibrillation	5 (0.9%)	5 (1.0%)	8 (2.0%)	23 (2.9%)	13 (1.4%)	28 (2.1%)
Syncope	4 (0.8%)	4 (0.8%)	4 (1.0%)	18 (2.2%)	8 (0.9%)	22 (1.7%)
Palpitations	1 (0.2%)	2 (0.4%)	0	14 (1.7%)	1 (0.1%)	16 (1.2%)
Tachycardia	0	1 (0.2%)	1 (0.3%)	10 (1.2%)	1 (0.1%)	11 (0.8%)
Bradycardia	0	1 (0.2%)	6 (1.5%)	6 (0.7%)	6 (0.6%)	7 (0.5%)
Loss of consciousness	1 (0.2%)	2 (0.4%)	0	2 (0.2%)	1 (0.1%)	4 (0.3%)
Supraventricular extrasystoles	2 (0.4%)	3 (0.6%)	2 (0.5%)	1 (0.1%)	4 (0.4%)	4 (0.3%)
Sinus tachycardia	0	1 (0.2%)	0	2 (0.2%)	0	3 (0.2%)
Ventricular extrasystoles	1 (0.2%)	3 (0.6%)	2 (0.5%)	0	3 (0.3%)	3 (0.2%)
Atrial flutter	1 (0.2%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Cardio-respiratory arrest	0	1 (0.2%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Supraventricular tachycardia	1 (0.2%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Ventricular tachycardia	0	0	0	2 (0.2%)	0	2 (0.2%)
Arrhythmia supraventricular	0	1 (0.2%)	0	0	0	1 (0.1%)
Heart rate increased	0	0	0	1 (0.1%)	0	1 (0.1%)
Sudden cardiac death	0	1 (0.2%)	0	0	0	1 (0.1%)
Ventricular fibrillation	0	1 (0.2%)	0	0	0	1 (0.1%)
Atrial tachycardia	1 (0.2%)	0	0	0	1 (0.1%)	0
Sudden death	2 (0.4%)	0	0	0	2 (0.2%)	0
Ventricular arrhythmia	0	0	1 (0.3%)	0	1 (0.1%)	0
Ischaemic Heart Disease	8 (1.5%)	23 (4.4%)	11 (2.8%)	30 (3.7%)	19 (2.1%)	53 (4.0%)
Angina pectoris	4 (0.8%)	9 (1.7%)	2 (0.5%)	13 (1.6%)	6 (0.6%)	22 (1.7%)
Myocardial infarction	0	5 (1.0%)	0	6 (0.7%)	0	11 (0.8%)
Coronary artery disease	0	0	1 (0.3%)	6 (0.7%)	1 (0.1%)	6 (0.5%)
Acute myocardial infarction	1 (0.2%)	3 (0.6%)	1 (0.3%)	2 (0.2%)	2 (0.2%)	5 (0.4%)
Arteriosclerosis coronary artery	1 (0.2%)	1 (0.2%)	1 (0.3%)	2 (0.2%)	2 (0.2%)	3 (0.2%)
Coronary artery occlusion	0	2 (0.4%)	0	1 (0.1%)	0	3 (0.2%)
Myocardial ischaemia	1 (0.2%)	1 (0.2%)	2 (0.5%)	2 (0.2%)	3 (0.3%)	3 (0.2%)
Acute coronary syndrome	1 (0.2%)	1 (0.2%)	3 (0.8%)	1 (0.1%)	4 (0.4%)	2 (0.2%)
Angina unstable	1 (0.2%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Coronary artery stenosis	0	2 (0.4%)	0	0	0	2 (0.2%)
Cardiac stress test abnormal	0	1 (0.2%)	0	0	0	1 (0.1%)
Silent myocardial infarction	0	0	0	1 (0.1%)	0	1 (0.1%)
Stress cardiomyopathy	0	0	1 (0.3%)	0	1 (0.1%)	0
Troponin increased	1 (0.2%)	0	0	0	1 (0.1%)	0
Cardiac Failure	10 (1.9%)	9 (1.7%)	4 (1.0%)	18 (2.2%)	14 (1.5%)	27 (2.0%)
Cardiac failure	5 (0.9%)	5 (1.0%)	0	6 (0.7%)	5 (0.5%)	11 (0.8%)
Cardiac failure congestive	2 (0.4%)	1 (0.2%)	1 (0.3%)	8 (1.0%)	3 (0.3%)	9 (0.7%)
Pulmonary oedema	1 (0.2%)	0	1 (0.3%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Acute left ventricular failure	0	1 (0.2%)	0	0	0	1 (0.1%)
Brain natriuretic peptide increased	0	1 (0.2%)	0	0	0	1 (0.1%)
Cardiac failure chronic	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Cardiogenic shock	0	1 (0.2%)	0	0	0	1 (0.1%)
Cardiomegaly	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Orthopnoea	0	0	0	1 (0.1%)	0	1 (0.1%)
Right ventricular dysfunction	0	0	0	1 (0.1%)	0	1 (0.1%)
Cardiac failure acute	0	0	1 (0.3%)	0	1 (0.1%)	0
Left ventricular failure	1 (0.2%)	0	0	0	1 (0.1%)	0
Nocturnal dyspnoea	0	0	1 (0.3%)	0	1 (0.1%)	0

Note: Percent is based on the Safety population.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0.

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Table 47: Treatment-emergent Cardiac Disorders by Presence of Cardiac Risk Factors Prior to Study Entry; Safety Population (Study 56021927PCR3002)

	Placebo	Apalutamide
Analysis set: Safety population	527	524
Subjects with a history of cardiac disorders, diabetes, or hypertension	320 (60.7%)	347 (66.2%)
Subjects with TEAE of cardiac disorders and history of cardiac disorders, diabetes, or hypertension	26 (4.9%)	32 (6.1%)
Subjects with TEAE of cardiac disorders but no prior history of cardiac disorders, diabetes, or hypertension	5 (0.9%)	14 (2.7%)

Key: TEAE=treatment-emergent adverse event.
Note: Percent is based on the Safety population.
Note: Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +30 days. For each category, subjects are counted only once, even if they experienced multiple events in that category.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities Version 20.0.
[TSFAE38.RTF] [JNJ-56021927\PCR3002\DBR_IA\RE_IA\PROD\TSFAE38.SAS] 31JAN2019, 12:43

Only 1 subject in the apalutamide + ADT arm discontinued treatment due to a TEAE of atrial fibrillation in SPARTAN.

QT Prolongation

A dedicated QT/QTc study (Study 56021927PCR1019) was conducted for apalutamide which showed that the upper bound of the 90% confidence interval for concentration dependent increase in QTcF at steady-state was below the threshold of 20 msec for anticancer agents.

In the combined population, for the TEAE of 'electrocardiogram QT prolonged', the exposure adjusted incidence (events per 100 P-Y) was 0.2 in the apalutamide + ADT arm and 0.1 in the placebo + ADT arm.

No TEAEs of torsades de pointe were reported in the combined population. Other events of which may represent sequelae from QT prolongation (cardio-respiratory arrest, ventricular tachycardia, sudden cardiac death, ventricular fibrillation, sudden death, and ventricular arrhythmia) occurred with a similar frequency and in less than 0.5% of patients in either arm of the combined population.

QT prolongation can also present as seizure; however, the 7 events of seizure that occurred in the combined population had alternative explanations and were not a result of QT prolongation.

QT prolongation can also present as syncope. In TITAN, the incidence of syncope was 0.8% in both arms. In SPARTAN, syncope was reported for 2.2% of patients in the apalutamide + ADT arm and 1.0% of patients in the placebo + ADT arm (the exposure adjusted incidence was 1.5 vs 0.9 events per 100 P-Y). None of the patients with TEAEs of syncope in SPARTAN had events of ventricular arrhythmia, ventricular fibrillation, or QTc prolongation reported. In the combined population, syncope was reported for 1.7% of patients in the apalutamide + ADT arm and 0.9% of patients in the placebo + ADT arm.

Ischemic Heart Disease

In TITAN, IHD was reported by more patients in the apalutamide + ADT arm (4.4%) than the placebo + ADT arm (1.5%); the exposure adjusted incidence was 3.6 vs 1.4 events per 100 P-Y. This finding accounts for the overall difference noted in TITAN between the arms for Cardiac Disorders. Of the events of ischemic heart disease, 10 events in the treatment arm were Grade 3 or 4, compared with 1 Grade 3 event in the control arm. In the apalutamide + ADT arm, 8 of the 10 patients with Grade 3 or 4 IHD were continuing with study treatment at the data cut-off. The number of fatal ischemic events was the same between treatment and control arms with 2 patients in each arm. Of the patients who had an ischemic event, most also had a medical history of cardiac disorders, hypertension, or diabetes (17 of 23 of patients in the treatment arm and 6 of 8 of patients in the control arm). Therefore, the difference in the

rate of IHD observed in TITAN cannot be explained by medical history. Additionally, of the patients who had an ischemic event, TEAEs of worsening or new onset hypertension, hypercholesterolemia, and hyperglycemia were reported for 30%, 13%, and 4% of patients respectively in the apalutamide + ADT arm. No such TEAEs were reported in the placebo + ADT arm. The median time to onset to an event of IHD was 403 days in the treatment arm as compared with 194 days in the control arm.

In SPARTAN, the incidence of IHD was 3.7% in the apalutamide + ADT arm and 2.8% in the placebo + ADT arm; the exposure adjusted incidence (event per 100 P-Y) was numerically lower in the in the treatment arm (2.7) as compared with the control arm (3.4). The grouped term of ischemic heart disease (IHD) was reported for 4.0% of patients in the apalutamide + ADT arm and 2.1% of patients in the placebo + ADT arm in the combined population (the exposure adjusted incidence was 3.1 vs 2.1 events per 100 P-Y).

Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with apalutamide and 2 patients (0.2%) treated with placebo died from an ischaemic heart disease.

Deaths

The incidence of fatalities due to cardiac disorders (including the grouped terms of cardiac failure, arrhythmia, and ischemic heart disease) was the same in both arms of the combined population (0.6%); the exposure adjusted incidence (events per 100 P-Y) was 0.4 in the apalutamide + ADT arm and 0.5 in the placebo + ADT arm.

Further, in the combined population:

- Fatal arrhythmias were reported in 0.2% of patients in the treatment arm and 0.3% of patients in the control arm.
- Fatal ischemic heart disease was reported in 0.5% of patients in the treatment arm and 0.2% of patients in the control arm; the exposure adjusted incidence was the same for both arms (0.2 events per 100 P-Y).
- Fatal cardiac failure was reported in the same proportion of patients in both arms (0.1%).

<u>Cerebrovascular Disorders (Ischemic Cerebrovascular Disorders and Hemorrhagic Cerebrovascular Disorders)</u>

Ischemic cerebrovascular disorders were reported for 1.5% of both arms of TITAN (2.2% in apalutamide arm vs 1.0% in placebo arm, the exposure adjusted incidence was 1.7 vs 0.9 events per 100 P-Y, in SPARTAN and 2.0% vs 1.3% in the combined population).The overall incidence of hemorrhagic cerebrovascular disorder was low with 0.4% in the treatment arm and 0.6% in the control arm (0.6% vs 0.3% in SPARTAN, 0.5% vs 0.4% in the combined population).

<u>Cognitive Deficits (memory impairment, amnesia, disturbance in attention and cognitive disorder)</u>

Patients receiving long-term ADT may be at risk for cognitive impairment. In TITAN, cognitive deficits were reported in 2.7% of the treatment arm and 1.5% of the control arm (the exposure adjusted incidence was 2.0 vs 1.2 events per 100- P-Y). In SPARTAN, cognitive deficits were reported for 5.2% of patients in the treatment arm and 3.0% of patients in the control arm (the exposure adjusted incidence was 3.5 vs 3.1 events per 100- P-Y). In the combined population, cognitive deficits were reported in 4.2% of the treatment arm and 2.2% of the control arm (exposure adjusted incidence was 2.9 vs 2.0 events per 100 P-Y). The majority of the events in the grouped term of cognitive deficits were Grade 1 or 2.

Table 48: Treatment-emergent Cognitive Deficits Adverse Events, Event Rate per 100 Subject-years of Exposure by Preferred Term; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: integrated safety	527	524	398	803	925	1327
Total Subject-years of exposure	731.9	830.4	447.0	1318.1	1178.9	2148.5
Number of distinct TE cognitive deficit adverse events	9 (1.2)	17 (2.0)	14 (3.1)	46 (3.5)	23 (2.0)	63 (2.9)
Preferred term						
Memory impairment	6 (0.8)	7 (0.8)	6 (1.3)	14 (1.1)	12 (1.0)	21 (1.0)
Amnesia	1 (0.1)	4 (0.5)	4 (0.9)	15 (1.1)	5 (0.4)	19 (0.9)
Cognitive disorder	1 (0.1)	5 (0.6)	3 (0.7)	7 (0.5)	4 (0.3)	12 (0.6)
Disturbance in attention	1 (0.1)	1 (0.1)	1 (0.2)	10 (0.8)	2 (0.2)	11 (0.5)

Key: TE = treatment-emergent
Note: Number in parentheses is event rate per 100 subject-years of exposure. Denominator is total subject years of exposure (total days of exposure/365.25) for the treatment group.
Numerator is number of distinct events with that preferred term.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.The event experienced by the subject with the worst toxicity grade is used.Adverse events are coded using MedDRA Version 20.0.
Note: Toxicity grade is based on NCI common toxicity criteria, version 4.03.
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Second Primary Cancer

TEAEs of a second primary cancer were reported in 4.0% of patients in the apalutamide + ADT arm and 2.8% of patients in the placebo + ADT arm in TITAN (6.2% vs 5.8% in SPARTAN and 5.4% vs 4.1% in the combined population). The 2 most commonly reported second primary cancers were basal cell carcinoma (1.4% apalutamide vs 1.0% placebo in the combined population) and squamous cell carcinoma (1.0% vs 0.2% in the combined population). No malignant or pre-malignant hematologic disorders were reported in either study. No signal for the development of a second primary cancer was identified with treatment with apalutamide.

Psychiatric disorders

Table 49: Number of Patients with Treatment-emergent Adverse Events Psychiatric disorders by System Organ Class and Preferred Term; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Psychiatric disorders	48 (9.1%)	56 (10.7%)	53 (13.3%)	146 (18.2%)	101 (10.9%)	202 (15.2%)
Insomnia	31 (5.9%)	24 (4.6%)	21 (5.3%)	55 (6.8%)	52 (5.6%)	79 (6.0%)
Anxiety	6 (1.1%)	9 (1.7%)	11 (2.8%)	31 (3.9%)	17 (1.8%)	40 (3.0%)
Depression	9 (1.7%)	6 (1.1%)	8 (2.0%)	29 (3.6%)	17 (1.8%)	35 (2.6%)
Depressed mood	1 (0.2%)	3 (0.6%)	5 (1.3%)	10 (1.2%)	6 (0.6%)	13 (1.0%)
Agitation	0	4 (0.8%)	2 (0.5%)	8 (1.0%)	2 (0.2%)	12 (0.9%)
Confusional state	4 (0.8%)	4 (0.8%)	0	7 (0.9%)	4 (0.4%)	11 (0.8%)
Sleep disorder	0	3 (0.6%)	3 (0.8%)	4 (0.5%)	3 (0.3%)	7 (0.5%)
Hallucination	0	1 (0.2%)	0	3 (0.4%)	0	4 (0.3%)
Irritability	0	0	1 (0.3%)	4 (0.5%)	1 (0.1%)	4 (0.3%)
Mood altered	3 (0.6%)	0	1 (0.3%)	4 (0.5%)	4 (0.4%)	4 (0.3%)
Nightmare	0	1 (0.2%)	0	3 (0.4%)	0	4 (0.3%)
Suicidal ideation	0	1 (0.2%)	0	3 (0.4%)	0	4 (0.3%)
Abnormal dreams	0	1 (0.2%)	0	2 (0.2%)	0	3 (0.2%)
Apathy	0	0	1 (0.3%)	3 (0.4%)	1 (0.1%)	3 (0.2%)
Affect lability	0	1 (0.2%)	0	1 (0.1%)	0	2 (0.2%)
Initial insomnia	0	2 (0.4%)	0	0	0	2 (0.2%)
Libido decreased	0	2 (0.4%)	0	0	0	2 (0.2%)
Major depression	0	0	0	2 (0.2%)	0	2 (0.2%)
Mental status changes	0	1 (0.2%)	0	1 (0.1%)	0	2 (0.2%)
Nervousness	0	1 (0.2%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Restlessness	0	1 (0.2%)	0	1 (0.1%)	0	2 (0.2%)
Adjustment disorder with depressed mood	0	0	0	1 (0.1%)	0	1 (0.1%)
Affective disorder	1 (0.2%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Aggression	0	0	0	1 (0.1%)	0	1 (0.1%)
Bruxism	0	0	0	1 (0.1%)	0	1 (0.1%)
Bulimia nervosa	0	0	0	1 (0.1%)	0	1 (0.1%)
Claustrophobia	1 (0.2%)	0	1 (0.3%)	1 (0.1%)	2 (0.2%)	1 (0.1%)
Delirium	0	0	2 (0.5%)	1 (0.1%)	2 (0.2%)	1 (0.1%)
Depressive symptom	0	0	0	1 (0.1%)	0	1 (0.1%)
Disorientation	0	0	0	1 (0.1%)	0	1 (0.1%)
Euphoric mood	0	1 (0.2%)	0	0	0	1 (0.1%)
Gastrointestinal somatic symptom disorder	0	1 (0.2%)	0	0	0	1 (0.1%)
Hallucination, visual	0	0	0	1 (0.1%)	0	1 (0.1%)
Middle insomnia	0	0	0	1 (0.1%)	0	1 (0.1%)
Mood swings	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Psychomotor retardation	0	0	0	1 (0.1%)	0	1 (0.1%)
Suicide attempt	0	1 (0.2%)	0	0	0	1 (0.1%)
Alcoholism	0	0	1 (0.3%)	0	1 (0.1%)	0
Emotional disorder	0	0	1 (0.3%)	0	1 (0.1%)	0
Loss of libido	0	0	1 (0.3%)	0	1 (0.1%)	0
Mania	1 (0.2%)	0	0	0	1 (0.1%)	0
Neurosis	1 (0.2%)	0	0	0	1 (0.1%)	0
Stress	0	0	1 (0.3%)	0	1 (0.1%)	0
Tic	1 (0.2%)	0	0	0	1 (0.1%)	0

Vital signs, physical findings and other observations related to safety

Weight Gain

Weight loss is an established ADR for apalutamide and weight gain is often seen with the initiation of ADT. In TITAN, where the majority of patients recently started ADT, the apalutamide-associated weight loss was manifested as less weight gain in the treatment arm as compared with the control arm. In SPARTAN, the apalutamide-associated weight loss was directly observed with the occurrence of more weight loss in the treatment arm as compared with the control arm.

In TITAN, a weight gain of 5%-20% from baseline occurred in 39% of apalutamide-treated patients and 46% of placebo-treated patients. Weight gain ≥ 20% from baseline was reported for 3.1% of apalutamide-treated patients and 2.9% of placebo-treated patients. An adverse event of weight increased was reported in 10% of apalutamide-treated patients vs 17% of placebo-treated patients in TITAN

Weight gain was less frequent in the SPARTAN study, where 10% of apalutamide-treated patients and 12% of placebo-treated patients had a weight gain of 5%-20% from baseline. Weight gain ≥ 20% from

baseline was reported for no apalutamide-treated patients and 0.3% of placebotreated patients. An adverse event of weight increased was reported in 3.1% of apalutamide treated patients and 2.3% of placebo-treated patients in SPARTAN.

In the combined population, 22% of apalutamide-treated patients and 31% of placebo-treated patients had a weight gain of 5-20% from baseline. A weight gain ≥ 20% from baseline was reported in 1.2% of apalutamide-treated patients and 1.7% of placebo-treated patients. An adverse event of weight increased was reported in 6.0% of apalutamide-treated patients and 11% of placebo-treated patients in the combined population.

Weight Loss

In TITAN, a higher proportion of apalutamide-treated patients (26%) compared with placebotreated patients (16%) had a weight loss of 5%-20% from baseline. A weight loss ≥ 20% from baseline was reported in 0.8% of apalutamide-treated patients and 1.3% of placebo-treated patients. An adverse event of weight decreased was reported in 6.5% of apalutamide-treated patients and 5.1% of placebo-treated patients in TITAN.

Weight loss was more frequent in the SPARTAN study, where 42% of apalutamide-treated patients and 19% of placebo-treated patients had a weight loss of 5%-20% from baseline. A weight loss ≥ 20% from baseline was reported in 1.9% of apalutamide-treated patients and 0.3% of placebo-treated patients. An adverse event of weight decreased was reported in 17% of apalutamide-treated patients and 6.3% of placebo-treated patients in SPARTAN.

In the combined population, 36% of apalutamide-treated patients and 17% of placebo-treated patients had a weight loss of 5%-20% from baseline. A weight loss ≥ 20% from baseline was reported in 1.5% of apalutamide-treated patients and 0.9% of placebo-treated patients. An adverse event of weight decreased was reported in 13% of apalutamide-treated patients and 5.6% of placebo-treated patients in the combined population.

Abnormalities in vital signs

Regarding systolic blood pressure and diastolic blood pressure, a higher percentage of patients showed >160 mmHg and increase from baseline >20 mmHg and >100 mmHg and increase from baseline >10 mmHg in apalutamide arm in both studies (see table below).

Table 50: Incidence of Abnormalities in Vital Signs; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
Analysis set: Integrated safety	Placebo 527	Apalutamide 524	Placebo 398	Apalutamide 803	Placebo 925	Apalutamide 1327
Systolic Blood Pressure						
N (no. subjects with baseline and any postbaseline measurement)	525 (99.6%)	520 (99.2%)	396 (99.5%)	800 (99.6%)	921 (99.6%)	1320 (99.5%)
< 90 mmHg and decrease from baseline > 20 mmHg	5 (1.0%)	1 (0.2%)	3 (0.8%)	6 (0.8%)	8 (0.9%)	7 (0.5%)
> 160 mmHg and increase from baseline > 20 mmHg	39 (7.4%)	59 (11.3%)	59 (14.9%)	146 (18.3%)	98 (10.6%)	205 (15.5%)
Diastolic Blood Pressure						
N (no. subjects with baseline and any postbaseline measurement)	525 (99.6%)	520 (99.2%)	396 (99.5%)	800 (99.6%)	921 (99.6%)	1320 (99.5%)
< 50 mmHg and decrease from baseline > 10 mmHg	8 (1.5%)	8 (1.5%)	4 (1.0%)	16 (2.0%)	12 (1.3%)	24 (1.8%)
> 100 mmHg and increase from baseline > 10 mmHg	22 (4.2%)	30 (5.8%)	18 (4.5%)	41 (5.1%)	40 (4.3%)	71 (5.4%)
Weight (kg)[a]						
N (no. subjects with baseline and any postbaseline measurement)	521 (98.9%)	513 (97.9%)	394 (99.0%)	794 (98.9%)	915 (98.9%)	1307 (98.5%)
5 to < 10% weight loss from baseline	61 (11.7%)	94 (18.3%)	51 (12.9%)	224 (28.2%)	112 (12.2%)	318 (24.3%)
10 to < 20% weight loss from baseline	21 (4.0%)	41 (8.0%)	24 (6.1%)	109 (13.7%)	45 (4.9%)	150 (11.5%)
>= 20% weight loss from baseline	7 (1.3%)	4 (0.8%)	1 (0.3%)	15 (1.9%)	8 (0.9%)	19 (1.5%)
N (no. subjects with baseline and any postbaseline measurement)	521 (98.9%)	513 (97.9%)	394 (99.0%)	794 (98.9%)	915 (98.9%)	1307 (98.5%)
5 to < 10% weight gain from baseline	144 (27.6%)	124 (24.2%)	43 (10.9%)	65 (8.2%)	187 (20.4%)	189 (14.5%)
10 to < 20% weight gain from baseline	95 (18.2%)	78 (15.2%)	6 (1.5%)	15 (1.9%)	101 (11.0%)	93 (7.1%)
>= 20% weight gain from baseline	15 (2.9%)	16 (3.1%)	1 (0.3%)	0	16 (1.7%)	16 (1.2%)

[a]Subject is included only once in weight loss at the maximum decrease level.
Note: N is the number of subjects with baseline and at least one postbaseline value for the specified vital sign parameter.
Note: Percentage calculation on N row is based on safety population of each treatment group as denominator. Percentage for abnormal row is calculated using the N row as denominator.

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Adverse Drug Reactions

In the initial submission for apalutamide, the following 11 terms were selected as ADRs based upon the review of 1,201 patients with NM-CRPC in the SPARTAN study: fatigue, arthralgia, skin rash, pruritus, seizure, hypercholesterolemia, hypertriglyceridemia, fracture, fall, weight decreased, and hypothyroidism.

In this submission, ADR selection was based upon the review of 1,051 patients with mCSPC in the TITAN study. A total of 30 TEAEs met the criteria of ≥1% higher absolute incidence in the apalutamide + ADT arm as compared with the placebo + ADT arm:

- Twelve (12) of these 30 terms were already defined as ADRs in the previous submission, either as an individual ADR or were part of a grouped ADR term (arthralgia, rash, pruritus, rash generalized, rash maculo-papular, erythema, fatigue, hypercholesterolaemia, hypertriglyceridaemia, weight decreased, blood thyroid stimulating hormone increased, hypothyroidism).
- Eighteen (18) of these 30 terms underwent medical evaluation by the Sponsor, which included review of the total incidence and exposure adjusted incidence as well as assessing the grouping of a term under a pre-existing SMQ or SOC.
  - Twelve (12) of these 18 terms were not selected to be ADRs: hyperhidrosis (3.4% apalutamide vs 1.7% placebo); dry skin (3.2% vs 1.5%); alopecia (2.3% vs 0.6%); abdominal pain upper (3.2% vs 2.1%); upper respiratory tract infection (6.5% vs 5.3%); sinusitis (1.7% vs 0.6%); hyperkalaemia (7.4% vs 5.1%); vitamin D deficiency (1.5% vs 0 %); headache (6.7% vs 5.5%); epistaxis (2.1% vs 0.6%); nasal congestion (1.5% vs 0.4%); leukopenia (5.0% vs 3.6%).

    For all 12 of these terms, no potential mechanism of action was identified and the difference in incidence between the two arms was small (< 2.5%). In the treatment arm, Grade 3 events were only reported for 4 of these terms and occurred at a low frequency: hyperhidrosis (0.4% apalutamide + ADT vs 0% placebo), hyperkalemia (0.6% vs 0.9%), headache (0.2% in both arms), and upper respiratory tract infection (0.2% in both arms). No Grade 4 events were reported
  - Five (5) of these 18 terms were included as ADR: muscle spasm, diarrhea, hot flush, hypertension and dysgeusia. Diarrhea, hot flush, hypertension and dysgeusia were not selected

as ADR in the initial submission as differences in exposure adjusted incidence [events/100 P-Y] between both arm (apalutamide and placebo) were low in SPARTAN study. A similar trend was observed in TITAN study. Therefore, its inclusion as ADR was considered at this moment.

- One (1) term (dermatitis) was added to the existing ADR grouped term of skin rash. In TITAN, the incidence of dermatitis was 1.5% in the apalutamide + ADT arm and 0.4% in the placebo + ADT arm. Dermatitis is likely another manifestation of the rash that has a dose-exposure relationship with apalutamide.

One additional term (ischemic heart disease) did not meet the ≥1% threshold but was still chosen as a new ADR (see discussion on AEs of special interest).

The most common adverse reactions are fatigue (26%), skin rash (26% of any grade and 6% Grade 3 or 4), hypertension (22%), hot flush (18%), arthralgia (17%), diarrhoea (16%), fall (13%), and weight decreased (13%). Other important adverse reactions include fractures (11%) and hypothyroidism (8%).

Table 51: Adverse Drug Reactions for Apalutamide

Preferred term(s)	Frequency Rates					
	Combined Population		TITAN		SPARTAN	
	Placebo +ADT	Apalutamide +ADT	Placebo +ADT	Apalutamide +ADT	Placebo +ADT	Apalutamide +ADT
Fatigue	19%	26%	17%	20%	21%	31%
Skin Rash[a,b]	7.7%	26%	8.9%	28%	6.0%	25%
Hypertension	18%	22%	16%	18%	20%	25%
Hot Flush	13%	18%	16%	23%	8.5%	14%
Arthralgia	12%	17%	15%	17%	8.3%	17%
Diarrhea	10%	16%	6.1%	9.4%	15%	21%
Weight decreased	5.6%	13%	5.1%	6.5%	6.3%	17%
Fall	8.0%	13%	7.0%	7.4%	9.3%	17%
Fracture[a]	5.7%	10%	4.6%	6.3%	7.3%	13%
Pruritus	3.2%	8.1%	4.6%	11%	1.5%	6.4%
Hypothyroidism[a]	1.5%	7.8%	1.1%	6.5%	2.0%	8.6%
Hypercholesterolemia	1.1%	5.7%	0.8%	4.6%	1.5%	6.4%
Dysgeusia	1.0%	5.6%	0.6%	3.2%	1.5%	7.1%
Muscle Spasms	1.8%	3.8%	1.9%	3.1%	1.8%	4.2%
Hypertriglyceridemia	1.1%	3.7%	1.3%	3.4%	0.8%	3.9%
Seizure[a]	0.2%	0.4%	0.4%	0.6%	0	0.2%
Ischemic Heart Disease[a]	2.1%	4.0%	1.5%	4.4%	2.8%	3.7%

Mod5.3.5.3/ISS/TableTSFAE02, Mod5.3.5.3/ISS/TableTSFAE19, Mod5.3.5.3/ISS/TableTSFAE50a, Mod5.3.5.3/ISS/TableTSFAE62

[a] Grouped Term

[b] Grouped Term of Skin Rash includes Dermatitis

Serious adverse event/deaths/other significant events

Deaths

The metastatic population in TITAN had a higher incidence of death (3.4% in the treatment arm and 4.4% in the control arm) as compared with the non-metastatic population in SPARTAN (1.6% in the treatment arm and 0.5% in the control arm).

Treatment-emergent Adverse Events Leading to Death

TEAEs leading to death were reported for 1.9% of patients in the apalutamide + ADT arm and 3.0% of patients in the placebo + ADT arm in TITAN (1.6% vs 0.5% in SPARTAN). In both studies, the most common SOC leading to death was Cardiac Disorders.

Table 52: Number of Patients with Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated Safety	527	524	398	803	925	1327
Subjects with 1 or more TEAEs leading to death	16 (3.0%)	10 (1.9%)	2 (0.5%)	13 (1.6%)	18 (1.9%)	23 (1.7%)
System organ class Preferred term						
Cardiac disorders	3 (0.6%)	4 (0.8%)	1 (0.3%)	3 (0.4%)	4 (0.4%)	7 (0.5%)
Acute myocardial infarction	1 (0.2%)	1 (0.2%)	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Cardio-respiratory arrest	0	1 (0.2%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Myocardial infarction	0	1 (0.2%)	0	1 (0.1%)	0	2 (0.2%)
Cardiogenic shock	0	1 (0.2%)	0	0	0	1 (0.1%)
Acute coronary syndrome	1 (0.2%)	0	0	0	1 (0.1%)	0
Cardiac failure	1 (0.2%)	0	0	0	1 (0.1%)	0
Infections and infestations	2 (0.4%)	0	0	5 (0.6%)	2 (0.2%)	5 (0.4%)
Sepsis	1 (0.2%)	0	0	3 (0.4%)	1 (0.1%)	3 (0.2%)
Pneumonia	0	0	0	2 (0.2%)	0	2 (0.2%)
Urosepsis	1 (0.2%)	0	0	0	1 (0.1%)	0
Nervous system disorders	1 (0.2%)	1 (0.2%)	0	2 (0.2%)	1 (0.1%)	3 (0.2%)
Cerebrovascular accident	0	1 (0.2%)	0	1 (0.1%)	0	2 (0.2%)
Cerebral haemorrhage	0	0	0	1 (0.1%)	0	1 (0.1%)
Haemorrhage intracranial	1 (0.2%)	0	0	0	1 (0.1%)	0
General disorders and administration site conditions	4 (0.8%)	1 (0.2%)	0	1 (0.1%)	4 (0.4%)	2 (0.2%)
Multiple organ dysfunction syndrome	0	0	0	1 (0.1%)	0	1 (0.1%)
Sudden cardiac death	0	1 (0.2%)	0	0	0	1 (0.1%)
Death	1 (0.2%)	0	0	0	1 (0.1%)	0
Hypothermia	1 (0.2%)	0	0	0	1 (0.1%)	0
Sudden death	2 (0.4%)	0	0	0	2 (0.2%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	2 (0.2%)	0	2 (0.2%)
Prostate cancer	0	0	0	2 (0.2%)	0	2 (0.2%)
Renal and urinary disorders	0	2 (0.4%)	0	0	0	2 (0.2%)
Acute kidney injury	0	2 (0.4%)	0	0	0	2 (0.2%)
Gastrointestinal disorders	0	1 (0.2%)	0	0	0	1 (0.1%)
Large intestinal ulcer perforation	0	1 (0.2%)	0	0	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	3 (0.6%)	1 (0.2%)	0	0	3 (0.3%)	1 (0.1%)
Respiratory failure	2 (0.4%)	1 (0.2%)	0	0	2 (0.2%)	1 (0.1%)
Pulmonary embolism	1 (0.2%)	0	0	0	1 (0.1%)	0
Injury, poisoning and procedural complications	1 (0.2%)	0	1 (0.3%)	0	2 (0.2%)	0
Road traffic accident	0	0	1 (0.3%)	0	1 (0.1%)	0
Subdural haemorrhage	1 (0.2%)	0	0	0	1 (0.1%)	0
Psychiatric disorders	1 (0.2%)	0	0	0	1 (0.1%)	0
Completed suicide	1 (0.2%)	0	0	0	1 (0.1%)	0
Vascular disorders	1 (0.2%)	0	0	0	1 (0.1%)	0
Vascular rupture	1 (0.2%)	0	0	0	1 (0.1%)	0

Key: TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.Adverse events are coded using MedDRA Version 20.0

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Serious Adverse Events

SAEs were reported for 20% of patients in the apalutamide + ADT arm and 20% of patients in the placebo + ADT arm in TITAN (27% vs 25% in SPARTAN). In TITAN, the most frequently reported SAEs (≥1% of patients in either arm) were fracture (as a grouped term), pneumonia, hematuria, urinary retention, spinal cord compression and back pain. Fracture (as a grouped term) was reported in 1.5% of patients in the apalutamide + ADT arm and 0.9% of patients in the placebo + ADT arm in TITAN.

Table 53: Number of Patients with Treatment-emergent Serious Adverse Events with Frequency of at Least 1% in Any Group by System Organ Class and Preferred Term; Integrated Safety

	56021927PCR3002		ARN-509-003		Combined	
	Placebo	Apalutamide	Placebo	Apalutamide	Placebo	Apalutamide
Analysis set: Integrated Safety	527	524	398	803	925	1327
Subjects with 1 or more treatment-emergent serious adverse events	107 (20.3%)	104 (19.8%)	98 (24.6%)	216 (26.9%)	205 (22.2%)	320 (24.1%)
System organ class Preferred term						
Infections and infestations	24 (4.6%)	21 (4.0%)	9 (2.3%)	50 (6.2%)	33 (3.6%)	71 (5.4%)
Pneumonia	3 (0.6%)	7 (1.3%)	2 (0.5%)	9 (1.1%)	5 (0.5%)	16 (1.2%)
Urinary tract infection	2 (0.4%)	4 (0.8%)	3 (0.8%)	11 (1.4%)	5 (0.5%)	15 (1.1%)
Renal and urinary disorders	25 (4.7%)	20 (3.8%)	44 (11.1%)	48 (6.0%)	69 (7.5%)	68 (5.1%)
Haematuria	3 (0.6%)	7 (1.3%)	8 (2.0%)	14 (1.7%)	11 (1.2%)	21 (1.6%)
Urinary retention	8 (1.5%)	4 (0.8%)	18 (4.5%)	11 (1.4%)	26 (2.8%)	15 (1.1%)
Hydronephrosis	4 (0.8%)	2 (0.4%)	8 (2.0%)	10 (1.2%)	12 (1.3%)	12 (0.9%)
Acute kidney injury	1 (0.2%)	2 (0.4%)	4 (1.0%)	6 (0.7%)	5 (0.5%)	8 (0.6%)
Urinary tract obstruction	0	3 (0.6%)	4 (1.0%)	2 (0.2%)	4 (0.4%)	5 (0.4%)
Renal failure	1 (0.2%)	0	4 (1.0%)	3 (0.4%)	5 (0.5%)	3 (0.2%)
Nervous system disorders	14 (2.7%)	10 (1.9%)	9 (2.3%)	24 (3.0%)	23 (2.5%)	34 (2.6%)
Spinal cord compression	6 (1.1%)	1 (0.2%)	1 (0.3%)	0	7 (0.8%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	18 (3.4%)	9 (1.7%)	5 (1.3%)	22 (2.7%)	23 (2.5%)	31 (2.3%)
Back pain	6 (1.1%)	2 (0.4%)	1 (0.3%)	2 (0.2%)	7 (0.8%)	4 (0.3%)

Note: Grade 5 events are not included.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 20.0

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Laboratory findings

Hematology

In study TITAN at baseline, the only Grade 3 or 4 hematologic abnormalities that occurred were Grade 3 neutrophils, which were reported in 2 patients (0.4%) in the apalutamide + ADT arm. During treatment, the most commonly reported Grade 3 abnormality was anemia (0.8% apalutamide vs 3.0% placebo). The only Grade 4 abnormalities were decreased neutrophils, which occurred in 3 apalutamide-treated patients (0.6%).

In study SPARTAN at baseline, there were no patients with Grade 3 or 4 hematologic abnormalities. During treatment, the most commonly reported Grade 3 abnormalities were decreased neutrophils (0.8% apalutamide vs 0.3% placebo) and anemia (0.5% apalutamide and 0.5% placebo). The only Grade 4

abnormalities that occurred were decreased neutrophils in 1 apalutamide-treated subject (0.1%) and decreased platelet count in 1 placebo-treated subject (0.3%).

In the combined population, during treatment, the majority of hematologic abnormalities were categorized as Grade 2 or lower. The most commonly reported Grade 3 abnormalities were anemia (0.6% apalutamide and 2.0% placebo) and decreased neutrophils (0.6% apalutamide and 0.2% placebo). The only Grade 4 abnormalities were decreased neutrophils in 4 apalutamide-treated patients (0.3%) and decreased platelet count in 1 placebo-treated subject (0.1%).

Chemistry

At baseline in TITAN, increased ALP, which is a common observation in patients with metastatic bone disease, was the most frequent Grade 3 or 4 laboratory abnormality (6.1% apalutamide vs 5.2% placebo). No other Grade 3 or 4 laboratory abnormalities occurred in >1% of patients at baseline in either arm. During treatment, the most frequent laboratory abnormalities (any grade) were: increased ALP (38% apalutamide vs 51% placebo); increased ALT (20% apalutamide vs 35% placebo); increased AST (18% apalutamide vs 36% placebo). During treatment, the most frequent Grade 3 or 4 laboratory abnormalities were: increased ALP (3.9% apalutamide vs 8.6% placebo); hyperkalemia (2.7% apalutamide vs 1.9% placebo); hypertriglyceridemia (2.6% apalutamide vs 2.5% placebo); hyponatremia (2.3% apalutamide vs 3.6% placebo).

At baseline in SPARTAN, no Grade 3 or 4 laboratory abnormality occurred in ≥ 0.3% of patients in either arm. During treatment, the most frequent laboratory abnormalities (any grade) were: high cholesterol (77% apalutamide vs 47% placebo); hypertriglyceridemia (69% apalutamide vs 51% placebo). During treatment, the most frequent Grade 3 or 4 laboratory abnormalities were: hyperkalemia (1.9% apalutamide vs 0.5% placebo); hypertriglyceridemia (1.9% apalutamide vs 0.8% placebo); hyponatremia (1.3% apalutamide vs 0.5% placebo); increased creatinine (0.5% apalutamide vs 1.3% placebo).

During treatment in the combined population, the most frequent laboratory abnormalities (any grade) were: high cholesterol (54% apalutamide vs 25% placebo); hypertriglyceridemia (51% apalutamide vs 32% placebo); increased ALP (22% apalutamide vs 35% placebo). During treatment, the most frequent Grade 3 or 4 laboratory abnormalities were: increased ALP (1.6% apalutamide vs 5.0% placebo); hyperkalemia (2.2% apalutamide vs 1.3% placebo); hyponatremia (1.7% apalutamide vs 2.3% placebo); hypertriglyceridemia (2.1% apalutamide vs 1.6% placebo).

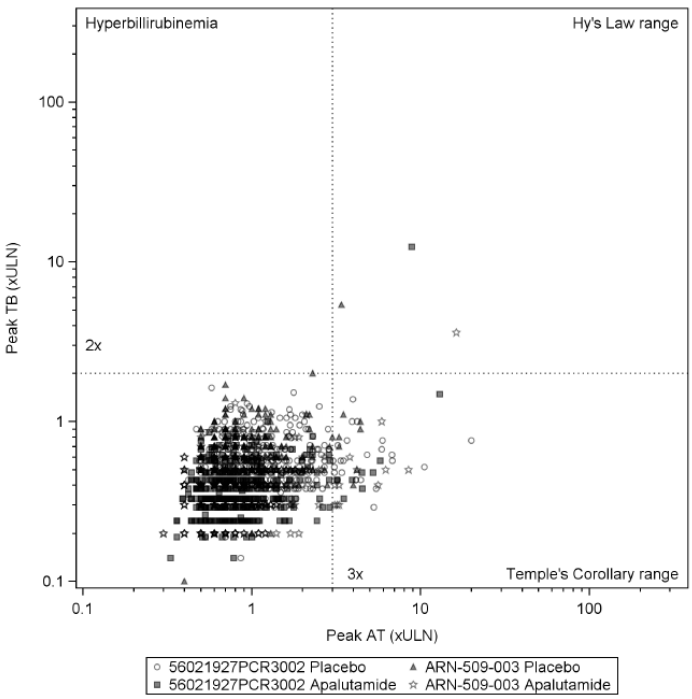
Hepatoxicity Laboratory Abnormalities

Table 54:**Incidence of Increased Liver Function Tests in TITAN and SPARTAN**

	TITAN		SPARTAN	
	Placebo + ADT	Apalutamide + ADT	Placebo + ADT	Apalutamide + ADT
Increased ALT				
Grade 1	30%	18%	18%	8.8%
Grade 2	3.4%	1.3%	1.3%	0.4%
Grade 3	1.0%	0.6%	0	0.4%
Grade 4	0	0	0	0
Increased AST				
Grade 1	31%	17%	14%	16%
Grade 2	3.2%	0.8%	1.0%	0.9%
Grade 3	1.1%	0.8%	0	0.4%
Grade 4	0	0	0	0
Increased Bilirubin				
Grade 1	3.6%	0.6%	5.1%	0.4%
Grade 2	0.6%	0.4%	0.5%	0
Grade 3	0.2%	0.2%	0.3%	0.1%
Grade 4	0	0	0	0
Increased ALP				
Grade 1	30%	29%	14%	12%
Grade 2	12%	5.6%	0.8%	0.3%
Grade 3	8.4%	3.5%	0.3%	0.1%
Grade 4	0.2%	0.4%	0	0

Source: Mod5.3.5.3/ISS/TableTSFLAB02

Six (6) patients met the eDISH laboratory criteria: in TITAN, 1 apalutamide-treated subject (with a history of chronic hepatitis B) and 3 placebo-treated patients, and in SPARTAN, 1 apalutamide-treated subject (with metastatic liver disease) and 1 placebo treated subject. Of these 6 patients, 2 patients met the laboratory criteria for Hy's Law: the 1 apalutamide treated subject (with a history of chronic hepatitis B) in TITAN and 1 placebo-treated subject in SPARTAN.



Peak TB=Peak Total Bilirubin; Peak AT=Maximum of (ALT, AST)
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Figure 15: Evaluation of Drug-induced Serious Hepatotoxicity (eDISH); Integrated Safety

Thyroid Stimulating Hormone (TSH)

For TSH, the change from baseline was greater for patients in the apalutamide + ADT arm as compared with patients in the placebo + ADT arm in TITAN (1.86 mIU/L vs 0.61 mIU/L), SPARTAN (2.01 mIU/L vs 0.60 mIU/L) and the combined population (1.96 mIU/L apalutamide vs 0.61 mIU/L placebo). The adverse event of special interest of hypothyroidism was more frequently reported in the apalutamide + ADT arm as compared with patients in the placebo + ADT arm (see AEs of special interest).

Safety in special populations

Intrinsic Factors

Age

In the combined population, 479 patients (21%) were < 65 years, 949 patients (42%) were 65 to 74 years, and 824 patients (37%) were ≥ 75 years. Patients were younger in the TITAN study (23% ≥ 75 years) as compared with the SPARTAN study (48% ≥ 75 years).

Table 55: Overall Safety Profile by Age; Integrated Safety (TITAN study)

	56021927PCR3002							
	Placebo				Apalutamide			
		Age				Age		
	Total	<65	65-74	≥75	Total	<65	65-74	≥75
Analysis set: Integrated Safety	527	182	232	113	524	148	243	133
Subjects with 1 or more:								
TEAEs[b]	509 (96.6%)	177 (97.3%)	220 (94.8%)	112 (99.1%)	507 (96.8%)	141 (95.3%)	233 (95.9%)	133 (100.0%)
Related TEAEs[a]	219 (41.6%)	71 (39.0%)	101 (43.5%)	47 (41.6%)	315 (60.1%)	78 (52.7%)	140 (57.6%)	97 (72.9%)
Grade 3-4 TEAEs	215 (40.8%)	81 (44.5%)	79 (34.1%)	55 (48.7%)	221 (42.2%)	58 (39.2%)	100 (41.2%)	63 (47.4%)
Related TEAEs[a]	31 (5.9%)	7 (3.8%)	16 (6.9%)	8 (7.1%)	66 (12.6%)	13 (8.8%)	29 (11.9%)	24 (18.0%)
Serious TEAEs[b]	107 (20.3%)	39 (21.4%)	42 (18.1%)	26 (23.0%)	104 (19.8%)	21 (14.2%)	48 (19.8%)	35 (26.3%)
Related serious TEAEs	4 (0.8%)	1 (0.5%)	3 (1.3%)	0	10 (1.9%)	2 (1.4%)	3 (1.2%)	5 (3.8%)
Grade 3-4 serious TEAEs	86 (16.3%)	32 (17.6%)	33 (14.2%)	21 (18.6%)	84 (16.0%)	17 (11.5%)	39 (16.0%)	28 (21.1%)
TEAEs leading to treatment discontinuation	28 (5.3%)	5 (2.7%)	11 (4.7%)	12 (10.6%)	42 (8.0%)	5 (3.4%)	19 (7.8%)	18 (13.5%)
Related TEAEs[a]	4 (0.8%)	1 (0.5%)	1 (0.4%)	2 (1.8%)	17 (3.2%)	3 (2.0%)	5 (2.1%)	9 (6.8%)
TEAEs leading to death	16 (3.0%)	2 (1.1%)	8 (3.4%)	6 (5.3%)	10 (1.9%)	2 (1.4%)	6 (2.5%)	2 (1.5%)
Related TEAEs[a]	0	0	0	0	0	0	0	0
All deaths on study[c]	23 (4.4%)	5 (2.7%)	10 (4.3%)	8 (7.1%)	18 (3.4%)	3 (2.0%)	9 (3.7%)	6 (4.5%)
Adverse event	16 (3.0%)	2 (1.1%)	8 (3.4%)	6 (5.3%)	10 (1.9%)	2 (1.4%)	6 (2.5%)	2 (1.5%)
Death due to prostate cancer	7 (1.3%)	3 (1.6%)	2 (0.9%)	2 (1.8%)	8 (1.5%)	1 (0.7%)	3 (1.2%)	4 (3.0%)
Other	0	0	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002 are considered as on study death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0

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Race

In the combined population, 1514 patients (74%) were white, 367 patients (18%) were Asian, 87 patients (4.3%) were black, and 73 patients (3.6%) were noted to have a race of other. The majority of patients in the TITAN and SPARTAN studies were white.

Table 56: Overall Safety Profile by Race; Integrated Safety (TITAN study)

	56021927PCR3002									
	Placebo					Apalutamide				
		Race					Race			
	Total	Asian	Black	White	Other	Total	Asian	Black	White	Other
Analysis set: Integrated Safety	519	110	9	365	35	513	118	10	354	31
Subjects with 1 or more:										
TEAEs[b]	501 (96.5%)	108 (98.2%)	8 (88.9%)	351 (96.2%)	34 (97.1%)	496 (96.7%)	114 (96.6%)	10 (100.0%)	341 (96.3%)	31 (100.0%)
Related TEAEs[a]	212 (40.8%)	57 (51.8%)	4 (44.4%)	144 (39.5%)	7 (20.0%)	306 (59.6%)	83 (70.3%)	5 (50.0%)	199 (56.2%)	19 (61.3%)
Grade 3-4 TEAEs	210 (40.5%)	44 (40.0%)	5 (55.6%)	150 (41.1%)	11 (31.4%)	214 (41.7%)	50 (42.4%)	6 (60.0%)	140 (39.5%)	18 (58.1%)
Related TEAEs[a]	30 (5.8%)	11 (10.0%)	0	18 (4.9%)	1 (2.9%)	60 (11.7%)	23 (19.5%)	1 (10.0%)	32 (9.0%)	4 (12.9%)
Serious TEAEs[b]	104 (20.0%)	27 (24.5%)	3 (33.3%)	71 (19.5%)	3 (8.6%)	102 (19.9%)	24 (20.3%)	2 (20.0%)	66 (18.6%)	10 (32.3%)
Related serious TEAEs	4 (0.8%)	2 (1.8%)	0	2 (0.5%)	0	9 (1.8%)	4 (3.4%)	1 (10.0%)	3 (0.8%)	1 (3.2%)
Grade 3-4 serious TEAEs	83 (16.0%)	24 (21.8%)	3 (33.3%)	54 (14.8%)	2 (5.7%)	82 (16.0%)	16 (13.6%)	2 (20.0%)	54 (15.3%)	10 (32.3%)
TEAEs leading to treatment discontinuation	28 (5.4%)	5 (4.5%)	1 (11.1%)	22 (6.0%)	0	41 (8.0%)	8 (6.8%)	2 (20.0%)	27 (7.6%)	4 (12.9%)
Related TEAEs[a]	4 (0.8%)	1 (0.9%)	0	3 (0.8%)	0	16 (3.1%)	4 (3.4%)	0	11 (3.1%)	1 (3.2%)
TEAEs leading to death	16 (3.1%)	3 (2.7%)	1 (11.1%)	12 (3.3%)	0	10 (1.9%)	0	0	8 (2.3%)	2 (6.5%)
Related TEAEs[a]	0	0	0	0	0	0	0	0	0	0
All deaths on study[c]	23 (4.4%)	4 (3.6%)	1 (11.1%)	18 (4.9%)	0	18 (3.5%)	2 (1.7%)	0	14 (4.0%)	2 (6.5%)
Adverse event	16 (3.1%)	3 (2.7%)	1 (11.1%)	12 (3.3%)	0	10 (1.9%)	0	0	8 (2.3%)	2 (6.5%)
Death due to prostate cancer	7 (1.3%)	1 (0.9%)	0	6 (1.6%)	0	8 (1.6%)	2 (1.7%)	0	6 (1.7%)	0
Other	0	0	0	0	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002 are considered as on study death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0

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Baseline ECOG Performance Status

In the combined population, 1606 patients (71%) had a baseline ECOG score of 0 and 645 patients (29%) had a baseline ECOG score of 1. Baseline ECOG scores were higher in TITAN as compared with SPARTAN.

Table 57: Overall Safety Profile by Baseline ECOG Performance Status; Integrated Safety (TITAN study)

	56021927PCR3002					
	Placebo			Apalutamide		
		Baseline ECOG Performance Status			Baseline ECOG Performance Status	
	Total	0	1	Total	0	1
Analysis set: Integrated Safety	526	348	178	524	327	197
Subjects with 1 or more:						
TEAEs[b]	508 (96.6%)	336 (96.6%)	172 (96.6%)	507 (96.8%)	319 (97.6%)	188 (95.4%)
Related TEAEs[a]	218 (41.4%)	155 (44.5%)	63 (35.4%)	315 (60.1%)	216 (66.1%)	99 (50.3%)
Grade 3-4 TEAEs	214 (40.7%)	133 (38.2%)	81 (45.5%)	221 (42.2%)	130 (39.8%)	91 (46.2%)
Related TEAEs[a]	31 (5.9%)	21 (6.0%)	10 (5.6%)	66 (12.6%)	42 (12.8%)	24 (12.2%)
Serious TEAEs[b]	106 (20.2%)	73 (21.0%)	33 (18.5%)	104 (19.8%)	61 (18.7%)	43 (21.8%)
Related serious TEAEs	4 (0.8%)	4 (1.1%)	0	10 (1.9%)	7 (2.1%)	3 (1.5%)
Grade 3-4 serious TEAEs	85 (16.2%)	56 (16.1%)	29 (16.3%)	84 (16.0%)	49 (15.0%)	35 (17.8%)
TEAEs leading to treatment discontinuation	28 (5.3%)	16 (4.6%)	12 (6.7%)	42 (8.0%)	26 (8.0%)	16 (8.1%)
Related TEAEs[a]	4 (0.8%)	2 (0.6%)	2 (1.1%)	17 (3.2%)	11 (3.4%)	6 (3.0%)
TEAEs leading to death	16 (3.0%)	9 (2.6%)	7 (3.9%)	10 (1.9%)	4 (1.2%)	6 (3.0%)
Related TEAEs[a]	0	0	0	0	0	0
All deaths on study[c]	23 (4.4%)	13 (3.7%)	10 (5.6%)	18 (3.4%)	10 (3.1%)	8 (4.1%)
Adverse event	16 (3.0%)	9 (2.6%)	7 (3.9%)	10 (1.9%)	4 (1.2%)	6 (3.0%)
Death due to prostate cancer	7 (1.3%)	4 (1.1%)	3 (1.7%)	8 (1.5%)	6 (1.8%)	2 (1.0%)
Other	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002 are considered as on study death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0

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Baseline PSA Value

Baseline PSA values were categorized as above the median and below the median.

Table 58: Overall Safety Profile by Baseline PSA Value; Integrated Safety (TITAN study)

	56021927PCR3002					
	Placebo			Apalutamide		
		Baseline PSA Value			Baseline PSA Value	
	Total	Below Median	Above Median	Total	Below Median	Above Median
Analysis set: Integrated Safety	527	286	241	524	239	285
Subjects with 1 or more:						
TEAEs[b]	509 (96.6%)	274 (95.8%)	235 (97.5%)	507 (96.8%)	235 (98.3%)	272 (95.4%)
Related TEAEs[a]	219 (41.6%)	118 (41.3%)	101 (41.9%)	315 (60.1%)	146 (61.1%)	169 (59.3%)
Grade 3-4 TEAEs	215 (40.8%)	99 (34.6%)	116 (48.1%)	221 (42.2%)	97 (40.6%)	124 (43.5%)
Related TEAEs[a]	31 (5.9%)	14 (4.9%)	17 (7.1%)	66 (12.6%)	34 (14.2%)	32 (11.2%)
Serious TEAEs[b]	107 (20.3%)	52 (18.2%)	55 (22.8%)	104 (19.8%)	44 (18.4%)	60 (21.1%)
Related serious TEAEs	4 (0.8%)	1 (0.3%)	3 (1.2%)	10 (1.9%)	6 (2.5%)	4 (1.4%)
Grade 3-4 serious TEAEs	86 (16.3%)	39 (13.6%)	47 (19.5%)	84 (16.0%)	34 (14.2%)	50 (17.5%)
TEAEs leading to treatment discontinuation	28 (5.3%)	12 (4.2%)	16 (6.6%)	42 (8.0%)	16 (6.7%)	26 (9.1%)
Related TEAEs[a]	4 (0.8%)	1 (0.3%)	3 (1.2%)	17 (3.2%)	8 (3.3%)	9 (3.2%)
TEAEs leading to death	16 (3.0%)	9 (3.1%)	7 (2.9%)	10 (1.9%)	2 (0.8%)	8 (2.8%)
Related TEAEs[a]	0	0	0	0	0	0
All deaths on study[c]	23 (4.4%)	12 (4.2%)	11 (4.6%)	18 (3.4%)	4 (1.7%)	14 (4.9%)
Adverse event	16 (3.0%)	9 (3.1%)	7 (2.9%)	10 (1.9%)	2 (0.8%)	8 (2.8%)
Death due to prostate cancer	7 (1.3%)	3 (1.0%)	4 (1.7%)	8 (1.5%)	2 (0.8%)	6 (2.1%)
Other	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002 are considered as on study death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0
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Extrinsic Factors

Geographic Region

In the combined population, 1360 patients (60%) were from North America or Europe and 892 patients (40%) were from the Rest of World region.. In TITAN, the majority of patients were from the Rest of World region, while in SPARTAN, the majority of patients were from North America or Europe.

Table 59: Overall Safety Profile by Geographic Region; Integrated Safety ((TITAN study)

	56021927PCR3002					
	Placebo			Apalutamide		
		Geographic Region			Geographic Region	
	Total	North America/Europe	Rest of the World	Total	North America/Europe	Rest of the World
Analysis set: Integrated Safety	527	173	354	524	173	351
Subjects with 1 or more:						
TEAEs[b]	509 (96.6%)	165 (95.4%)	344 (97.2%)	507 (96.8%)	168 (97.1%)	339 (96.6%)
Related TEAEs[a]	219 (41.6%)	89 (51.4%)	130 (36.7%)	315 (60.1%)	121 (69.9%)	194 (55.3%)
Grade 3-4 TEAEs	215 (40.8%)	72 (41.6%)	143 (40.4%)	221 (42.2%)	68 (39.3%)	153 (43.6%)
Related TEAEs[a]	31 (5.9%)	13 (7.5%)	18 (5.1%)	66 (12.6%)	29 (16.8%)	37 (10.5%)
Serious TEAEs[b]	107 (20.3%)	43 (24.9%)	64 (18.1%)	104 (19.8%)	27 (15.6%)	77 (21.9%)
Related serious TEAEs	4 (0.8%)	2 (1.2%)	2 (0.6%)	10 (1.9%)	4 (2.3%)	6 (1.7%)
Grade 3-4 serious TEAEs	86 (16.3%)	35 (20.2%)	51 (14.4%)	84 (16.0%)	25 (14.5%)	59 (16.8%)
TEAEs leading to treatment discontinuation	28 (5.3%)	10 (5.8%)	18 (5.1%)	42 (8.0%)	14 (8.1%)	28 (8.0%)
Related TEAEs[a]	4 (0.8%)	1 (0.6%)	3 (0.8%)	17 (3.2%)	6 (3.5%)	11 (3.1%)
TEAEs leading to death	16 (3.0%)	3 (1.7%)	13 (3.7%)	10 (1.9%)	2 (1.2%)	8 (2.3%)
Related TEAEs[a]	0	0	0	0	0	0
All deaths on study[c]	23 (4.4%)	4 (2.3%)	19 (5.4%)	18 (3.4%)	3 (1.7%)	15 (4.3%)
Adverse event	16 (3.0%)	3 (1.7%)	13 (3.7%)	10 (1.9%)	2 (1.2%)	8 (2.3%)
Death due to prostate cancer	7 (1.3%)	1 (0.6%)	6 (1.7%)	8 (1.5%)	1 (0.6%)	7 (2.0%)
Other	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002 are considered as on study death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003, and within 30 days of last dose of study drug for studies 56021927PCR3002. For each category, subjects are counted only once, even if they experienced multiple events in that category.Adverse events are coded using MedDRA Version 20.0
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Discontinuation due to adverse events

Adverse Events Leading to Discontinuation of Study Drug

The incidence of TEAEs leading to treatment discontinuation was higher in apalutamide + ADT arm as compared with placebo + ADT arm in TITAN (8.0% vs 5.3%), SPARTAN (11% vs 7.8%) and the combined population (10% apalutamide vs 6.4% placebo). Skin rash (as a grouped term) was the most common TEAE leading to treatment discontinuation, occurring in 1.5% of patients in the apalutamide + ADT arm and 0.2% of patients in the placebo + ADT arm in the combined population (2.4% vs 0% in SPARTAN and 2.0% vs 0.1% in the combined population). Fatigue was the next most common TEAE leading to treatment discontinuation occurring in 0.8% of patients in the apalutamide + ADT arm and 0% of patients in the placebo + ADT arm in TITAN (1.1% vs 0.3% in SPARTAN and 1.0% vs 0.1% in the combined population). All other TEAEs leading to treatment discontinuation occurred at a low percentage (≤0.5%) in both studies.

Adverse Events Leading to Dose Modification and Dose reduction

The incidence of TEAEs leading to dose reduction or interruption was higher in apalutamide + ADT arm as compared with placebo + ADT arm in TITAN (23% vs 13%), SPARTAN (33% vs 19%) and the combined population (29% apalutamide vs 15% placebo). The same applies to the incidence of TEAEs leading to dose reduction: 7.1% in apalutamide + ADT arm as compared with 2.1% in placebo + ADT arm in TITAN (in SPARTAN: 9.5% vs 1.8%; in the combined population: 8.5% apalutamide vs 1.9% placebo).

Skin Rash (grouped term) was the most common reason for dose reduction or interruption in the apalutamide + ADT arm in both studies. In the apalutamide + ADT arm of TITAN, a higher proportion of patients had a dose interruption (7.4%) or dose reduction (4.8%) due to skin rash as compared with the proportion of patients who discontinued treatment due to skin rash (1.5%). A similar trend was noted in the apalutamide + ADT arm of SPARTAN, where 6.7% of patients had a dose interruption, 2.7% of patients had a dose reduction, and 2.4% of patients discontinued treatment due to skin rash.

In SPARTAN, fatigue was the next most common TEAE leading to treatment reduction, occurring in 1.7% of patients in the apalutamide + ADT arm and 0% of patients in the placebo + ADT arm. (In TITAN, fatigue led to treatment reduction in 0.4% of patients in the treatment arm and 0% of patients in the control arm.). All other TEAEs leading to treatment reduction occurred at a low percentage (≤0.6%) in both studies.

Adverse Events Leading to Dose Interruption

The incidence of TEAEs leading to dose interruption was higher in apalutamide + ADT arm as compared with placebo + ADT arm in TITAN (20% vs 12%), SPARTAN (31% vs 18%) and the combined population (26% apalutamide vs 15% placebo). In TITAN, the most frequently reported TEAEs leading to interruption of treatment (reported for >1% of patients in either arm) were: skin rash (grouped term): 7.4% apalutamide vs 0.8% placebo; fatigue: 1.1% apalutamide vs 0.4% placebo and hypertension: 1.1% apalutamide vs 1.1% placebo. In SPARTAN, the most frequently reported TEAEs leading to interruption of treatment (reported for >1% of patients in either arm) were: skin rash (grouped term): 6.7% apalutamide vs 1.3% placebo; diarrhea: 2.5% apalutamide vs 1.3% placebo; fatigue: 2.2% apalutamide vs 0.5% placebo; nausea: 1.6% apalutamide vs 1.0% placebo; hypertension: 1.2% apalutamide vs 0.8% placebo; vomiting: 1.2% apalutamide vs 1.0% placebo; hematuria: 1.1% apalutamide vs 0.5% placebo; urinary tract infection: 0.6% apalutamide vs 1.3% placebo.

Post marketing experience

Based on the 1,441,320 60 mg tablets distributed worldwide from launch to 31 October 2018, the estimated exposure to apalutamide is 360,330 person-days, or 12,011 person-months, or 1,001 person-years. Postmarketing surveillance of spontaneously reported AEs is ongoing. The surveillance of spontaneous cases of AEs reported with the use of apalutamide indicates that the safety profile of the drug in post-marketing use is consistent with what is known about the drugs overall established safety profile from clinical studies.

2.5.1. Discussion on clinical safety

The safety population included data from 2 randomized, multicenter, placebo-controlled, Phase 3 studies (TITAN and SPARTAN) in where apalutamide 240 mg was added to ADT in men with prostate cancer. Study TITAN is submitted as pivotal study in the current application for the new indication in mCSPC patients while study SPARTAN was submitted in the initial authorization for apalutamide in nmCRPC patients.

Apart from expected differences due to disease characteristics (mCSPC vs NM-CRPC) and slightly worse ECOG performance status *(ECOG1: 38% apalutamide vs 34% placebo in TITAN and 23% vs 23% in SPARTAN)* and Gleason score *(>7: 67% apalutamide vs 68% placebo in TITAN and 43% vs 44% in SPARTAN)* for TITAN population than for SPARTAN, it should be pointed out that patients in TITAN were younger *(median age 68 years vs 74 years)*, weighed less *(median weight 77 Kg vs 84 kg)* and history of cardiac disorders, diabetes or hypertension was slightly lower than patients in SPARTAN *(66% apalutamide and 61% placebo in TITAN; 75% vs 76% in SPARTAN)*. Additionally, in TITAN, although all mCSPC patients received at least 1 prior treatment for prostate cancer and hormone therapy, time from diagnostic *(median 0.34 years in both arms in TITAN; 7.85 apalutamida vs 7.94 placebo in SPARTAN)* and exposure to prior ADT course *(71% received prior ADT for 3 months or less prior to randomization)* was short, being proportion of patients with prior surgery or radiotherapy low (16% in TITAN vs 77% in SPARTAN). It is noted that majority of patients in TITAN study had metastasis at initial diagnosis (83.7% in apalutamide and 78.4% in placebo). All these facts might have a relevant impact on observed safety results in each study.

The median duration of treatment was 20 months for the apalutamide arms in both studies being lower in placebo arms *(18 months in TITAN and 11 months in SPARTAN)*. To adjust for the time on treatment, the event rate of AEs per 100 patient-years (P-Y) of exposure was also analysed.

Study drug compliance was higher in TITAN study while discontinuations and dose adjustments were higher in SPARTAN study. The highest rate of treatment discontinuation was mainly due to progressive disease in both studies, being higher in placebo arms. Slightly higher rate of treatment discontinuation due to progressive disease was observed in SPARTAN, although several deaths should be considered as reason for termination in TITAN vs none in SPARTAN. Treatment discontinuation due to AEs was more common in the apalutamide arm than with the placebo arm but occurred less frequently in TITAN (7.4% apalutamide vs 3.2% placebo) than in SPARTAN (11% vs 6.5%). Skin rash (grouped term) was the most common reason for treatment discontinuation in the apalutamide arm in both studies.

Almost all patients in TITAN and SPARTAN were reported to have at least 1 or more TEAE (>93% across all groups). In TITAN, the most frequently reported TEAEs (≥15% of patients in either arm) was skin rash (grouped term), fatigue, back pain, hypertension, arthralgia, hot flush and weight increased. Apart from hot flush and weight increased, the rest TEAEs were also frequently reported TEAEs in SPARTAN. Most of these events were Grade 1 or 2. With the exception of skin rash (grouped term), these events seldom led to treatment discontinuation (≤1.5%) or dose modification and were rarely considered to be SAEs

(≤1.1%). Except for back pain which was not considered drug related by investigator, all of these frequently reported TEAEs are ADRs for apalutamide (see SmPC section 4.8).

Grade 3-4 TEAEs were reported for 42% of patients in the apalutamide arm and 41% of patients in the placebo arm in TITAN (47% vs 35% in SPARTAN). In TITAN, the most frequently reported Grade 3 or 4 TEAEs (≥3% of patients in either arm) were hypertension, skin rash (grouped term) and anemia. Hypertension and skin rash were also among the most frequently reported Grade 3 or 4 TEAEs (≥3% of patients in either arm) in SPARTAN.

SAEs were reported for 20% of patients in the apalutamide arm and 20% of patients in the placebo arm in TITAN (27% vs 25% in SPARTAN). In TITAN, the most frequently reported SAEs (≥1% of patients in either arm) were grouped term of fracture (1.5% apalutamide vs 0.9% placebo), pneumonia, hematuria, urinary retention, spinal cord compression and back pain. Apart from spinal cord compression and back pain, these TEAEs were also observed as SAEs in SPARTAN.

TEAEs leading to death were reported for 1.9% of patients in the apalutamide arm and 3.0% of patients in the placebo arm in TITAN (1.6% vs 0.5% in SPARTAN). In both studies, the most common SOC leading to death was Cardiac Disorders (acute myocardial infarction, cardio-respiratory arrest, myocardial infarction, cardiogenic shock in apalutamide arm). Deaths were reported for 3.4% of patients in the apalutamide arm and 4.4% of patients in the placebo arm in TITAN (1.6% vs 0.5% in SPARTAN).

Treatment was discontinued due to a TEAE in 8.0% of patients in the apalutamide arm and 5.3% of patients in the placebo arm in TITAN (11% vs 7.8% in SPARTAN). Skin rash (as a grouped term) was the most common TEAE leading to treatment discontinuation (1.5% apalutamide vs 0.2% placebo in TITAN and 2.4% vs 0% in SPARTAN). Fatigue was the next most common TEAE leading to treatment discontinuation (0.8% vs 0% in TITAN and 1.1% vs 0.3% in SPARTAN).

Skin Rash (grouped term) was the most common reason for dose reduction or interruption in the apalutamide + ADT arm in both studies. Recommendations for handling skin rash appear adequate since number of discontinuations in the apalutamide arm due to skin rash were lower than dose reductions or dose interruptions in both studies (7.4% dose interruption or 4.8% dose reduction vs 1.5% discontinuation in TITAN and 6.7% dose interruption or 2.7% dose reduction vs 2.4% discontinuation in SPARTAN)

Higher incidence of all AEs of special interest (skin rash, fall, fracture, seizure and hypothyroidism) was reported with apalutamide in comparison with placebo in both studies. The incidence of these AEs is similar in both studies except for fall and fracture. The mHSPC population in TITAN was younger and had a shorter duration of ADT exposure than the nmCRPC population in SPARTAN which may contribute to the lower incidence of fractures with apalutamide in TITAN. In any case, the incidences of fall and fracture were higher with apalutamide than with placebo.

Other adverse event of special interest for apalutamide are cardiac disorders (including cardiac failure, arrhythmia, ischemic heart disease and deaths), cerebrovascular disorders (including ischemic cerebrovascular disorders and hemorrhagic cerebrovascular disorders), cognitive deficits (including memory impairment, amnesia, disturbance in attention and cognitive disorder) and second primary cancer.

With regards to cardiac disorders, multiple observational studies have shown that men treated with ADT have increased risk of cardiovascular morbidity and mortality. The cardiotoxicity of ADT was confirmed in a population-based study suggesting a slightly elevated myocardial infarction risk regardless of existing cardiovascular disease (CVD) history (Keating2013), though other studies suggested that CVD-specific and all-cause mortality only occurred in patients with pre-existing CVD (Nanda 2014, Ziehr 2015).

Patients in the TITAN and SPARTAN studies were exposed to ADT, which was the background therapy for all patients in these studies. However, the underlying baseline factors were different between the populations enrolled in these two studies as mentioned above.

Patients with clinically significant cardiovascular disease in the past 6 months including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischaemic attacks), or clinically significant ventricular arrhythmias were excluded from the clinical studies (see SmPC section 4.4).

The overall rate of cardiac disorders was slightly lower in TITAN *(8.8% apalutamide vs 5.9% placebo)* in comparison with SPARTAN *(13% apalutamide vs 9.5% placebo)*. This may be justified by differences in age, weight, exposure to ADT and history of cardiac risk factors in the populations of both studies. However, although incidence of cardiac disorders was lower in study TITAN, it was still higher for apalutamide arm vs the placebo arm even in the group without history of cardiac risk factors prior to study entry (see Table 47).

Main differences in cardiac disorders are led by ischemic heart disease. The term ischemic heart disease includes angina pectoris, myocardial infarction, acute myocardial infarction, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, arteriosclerosis coronary artery, cardiac stress test abnormal, myocardial ischaemia, angina unstable and troponin increased. Based upon the available data and analyses, ischemic heart disease has been added as an ADR in the SmPC section 4.8. Section 4.4. of the SmPC also reflects that ischaemic heart disease, including events leading to death, occurred in patients treated with apalutamide. The majority of patients had cardiac risk factors. Patients should be monitored for signs and symptoms of ischaemic heart disease and management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia should be optimised as per standard of care. (see SmPC section 4.4). Ischemic heart disease has been added as important identified risk in the list of safety concerns in the RMP.

Regarding QT prolongation, the applicant has discussed events of torsade de pointes, syncope, seizure, sudden death, sudden cardiac death, ventricular tachycardia and ventricular fibrillation/flutter. QT prolongation is already included as an ADR in section 4.8 of the SmPC.

For arrhythmias, even when differences are small between arms in TITAN, SPARTAN and the combined population, there is an overall trend to higher incidence in apalutamide arm.

Incidence of cardiac failure and deaths due to cardiac events seems to be similar in both arms in TITAN study.

Although a causal relationship between apalutamide and arrhythmias, cardiac failure, and deaths due to cardiac events cannot be established since data are limited, it cannot be fully ruled out at this stage and the MAH should continue to closely monitor these events and report when submitting the final CSR.

Differences on secondary primary cancer, cognitive deficit and cerebrovascular disorders between arms were small. Although a causal relationship between apalutamide and these adverse events cannot be established since data are limited, it cannot be fully ruled out at this stage and the MAH should continue to closely monitor these events.

Although differences between both arms in TITAN study in terms of Psychiatric disorders were small, there was an overall trend to higher incidence with apalutamide than with placebo. The event rate of psychiatric disorders when adjusted for exposure was similar between arms in both studies. Alternate explanations for five SAEs in apalutamide arm seem to be reasonable.

Overall, the MAH should continue to monitor secondary primary cancer, cognitive deficit, cerebrovascular disorders, psychiatric disorders and discuss these events when submitting the final OS analysis.

Section 4.8 of the SmPC has been updated to reflect updated safety information. Thirty TEAEs were assessed as potential ADR. Among these, 12 were already included in the SmPC as ADR, 5 have been added as ADR *(muscle spasm, diarrhea, hot flush, hypertension and dysgeusia),* and 1 has been added to the existing ADR group of skin rash *(dermatitis)*.

Twelve adverse events have not been selected as ADRs (see section on ADRs) because no potential mechanism of action was identified and the difference in incidence between the two arms was small (< 2.5%). However, for some of these events, the difference in incidence between arms was higher than double for apalutamide in comparison with placebo (hyperhidrosis, dry skin, alopecia, sinusitis, epistaxis and nasal congestion). Despite no clear mechanism of action identified, some of these events can be considered partly in line with cutaneous toxicity observed with apalutamide. Although there is insufficient data to establish a causal relationship with apalutamide, it cannot be fully ruled out at this stage and the MAH is requested to further discuss these TEAEs when submitting updated safety data together with the final OS analysis.

Regarding laboratory findings, and despite the fact that number of events is very limited, further discussion was requested on hyperkalemia and decreasing of neutrophils. Exposure-adjusted event rates were similar in both arm for leukopenia and neutropenia. However, the incidence for hyperkalaemia was slightly higher with apalutamide even after exposure adjustment. Although a causal relationship between apalutamide and hyperkalaemia cannot be established, it cannot be fully ruled out at this stage and the MAH is requested to further discuss the risk of hyperkalaemia when providing the updated safety data together with the final OS analysis.

Overall, the incidence of the events, especially TEAEs, Grade 3-4 TEAEs, Serious TEAEs, were higher in patients ≥ 75 years as compared with ≤ 65 years and 65 to 74 years in both studies. Similar trend was observed for patients with baseline ECOG score of 1 in comparison with patients with an ECOG score of 0. However, this last finding is less marked on TITAN study, probably because the population has been overall less pretreated.

In a country specific analysis, it was noted that the incidence of the grouped term of skin rash in the apalutamide + ADT arm was approximately double in Japan as compared with the entire study population in both studies (approximately 50% apalutamide vs 25% placebo). This observed difference in the incidence of skin rash between the Japanese population and the entire study population was not fully explained by differences in exposure.

The SmPC has been updated to reflect the safety information available in mHSPC and include an additional warning on ischemic heart disease. No additional pharmacovigilance activities were considered needed as a result of the present procedure (see RMP).

2.5.2. Conclusions on clinical safety

Safety results in TITAN study are overall in line with the known safety profile of apalutamide (mainly based on SPARTAN study). However, based on results of TITAN, six TEAEs have been added as ADRs [ischemic heart disease, muscle spasm, diarrhoea, hot flush, hypertension, dysgeusia and dermatitis (in skin rash groped term)] to the ADRs established based on the results of SPARTAN study. Furthermore, a warning about the risk of ischemic heart disease has been included in the SmPC.

The MAH is recommended to submit updated safety data together with the final OS analysis of study TITAN (REC). The MAH should continue to monitor events of arrhythmias, cardiac failure, deaths due to cardiac events, secondary primary cancer, cognitive deficit, cerebrovascular disorders, psychiatric disorders, hyperhidrosis, dry skin, alopecia, sinusitis, epistaxis and hyperkalaemia and report on these events when submitting the updated safety analysis from study TITAN.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 2.3 with the following content:

Safety concerns

Table 59. Summary of the Safety Concerns

Important identified risks	Seizures Fall Non-pathological fracture Ischemic heart disease
Important potential risks	None
Missing information	Use in patients with severe hepatic impairment Use in patients with clinically significant cardiovascular disease Carcinogenic potential

Pharmacovigilance plan

Table 60. Summary Table of Additional Pharmacovigilance Activities

Trial Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
56021927PCR1026 A single-dose, open-label study to evaluate the pharmacokinetics of apalutamide in subjects with severe hepatic impairment compared with subjects with normal hepatic function. Planned	To characterize the single dose PK and safety of apalutamide in subjects with severe hepatic impairment relative to subjects with normal hepatic function.	Use in patients with severe hepatic impairment	Protocol submission Study start Final results Final report	September 2019 January 2020 31 March 2022 31 January 2023

Trial Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A feasibility assessment of a prospective, observational safety study to characterize the risks of the use of apalutamide in NM-CRPC patients on ADT with clinically significant cardiovascular conditions. Planned	To better characterize the risks of use of apalutamide in the subgroup of patients with clinically significant cardiovascular disease.	Use in patients with clinically significant cardiovascular disease	Feasibility assessment report Final results Final report	Submitted 29 March 2019 30 April 2023 31 August 2023
TOX11338 A 2-year carcinogenicity study of JNJ-56021927-AAA by oral gavage in rats. Ongoing	To better characterize the carcinogenic potential of apalutamide.	Carcinogenic potential	Final report	30 September 2021
TOX13540 A 26-week carcinogenicity study of JNJ-56021927-AAA by oral gavage in CByB6F1/Tg.rasH2 hemizygous mice. Ongoing	To better characterize the carcinogenic potential of apalutamide.	Carcinogenic potential	Final report	30 September 2020

Risk minimisation measures

Table 61. Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Seizures	Routine risk minimization measures: • SmPC Section 4.4;4.7;4.8 • PL Section 2;4 • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • TFUQ to obtain structured information on reported suspected adverse reaction of seizures Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Fall	Routine risk minimization measures: • SmPC Section 4.4;4.8 • PL Section 2;4 • PL Section 4 • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • TFUQ to obtain structured information on reported suspected adverse reaction of fall Additional pharmacovigilance activities: • None
Non-pathological fracture	Routine risk minimization measures: • SmPC Section 4.4;4.8 • PL Section 2;4 • PL Section 4 • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • TFUQ to obtain structured information on reported suspected adverse reaction of fractures Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Ischemic heart disease	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic heart disease is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of cardiovascular risk factors is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of heart disease is provided in PL Section 2 and PL Section 4 • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information		
Use in patients with severe hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 5.2 • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • 56021927PCR1026 Final report: 31 January 2023

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with clinically significant cardiovascular disease	Routine risk minimization measures: • SmPC Section 4.4 • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • A feasibility assessment of a prospective, observational safety study to characterize the risks of the use of apalutamide in NM-CRPC patients on ADT with clinically significant cardiovascular conditions Feasibility assessment report: submitted 29 March 2019 Final report: 31 August 2023
Carcinogenic potential	Routine risk minimization measures: • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Nonclinical study TOX11338 Final report: 30 September 2021 • Nonclinical study TOX13540 Final report: 30 September 2020

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. Particularly, a warning on ischaemic cardiovascular events and new safety and efficacy information are included in the SmPC. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to make editorial update to the SmPC and Labelling. The RMP version 2.3 is approved.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the variation has no relevant impact on the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).

For patients with this advanced stage of the disease, the aim of treatment is to improve the symptoms in particular pain and to extend the time during which the disease can be controlled with androgen deprivation therapy to delay progression.

3.1.2. Available therapies and unmet medical need

Initial treatments for both locally advanced and metastatic prostate cancer have been ADT defined as surgical castration by bilateral orchiectomy or medical castration with gonadotropin-releasing hormone (GnRH) agonists or antagonists.

Docetaxel (75 mg/m^2 every 3 weeks for 6 cycles) has been shown to improve overall survival (OS) and failure-free survival (FFS) in patients with mHSPC in multiple studies, including CHAARTED and Arm C of the STAMPEDE trial and has been recently approved for the treatment of mHSPC.

In 2017, abiraterone in combination with ADT and prednisone or prednisolone was authorised in EU for the treatment of adult men with newly diagnosed high risk metastatic hormone sensitive prostate cancer.

3.1.3. Main clinical studies

Efficacy data in support of this application were mainly provided from trial 56029127PCR3002 (TITAN), a Phase 3 randomized, placebo-controlled, double-blind study of apalutamide plus ADT versus ADT alone in 1,051 patients with mHSPC. Patients were excluded if the site of metastases was limited to either the lymph nodes or viscera (e.g., liver or lung). Patients with both high- and low-volume mHSPC were eligible for the study. All patients in the TITAN trial received concomitant GnRH analog or had prior bilateral orchiectomy. Around 11% of patients received prior treatment with docetaxel (maximum of 6 cycles, last dose ≤2 months prior to randomisation and maintained response prior to randomisation). 16% of patients had prior surgery, radiotherapy of the prostate or both. 68% of patients received prior treatment with a first-generation anti-androgen in the non-metastatic setting.

The TITAN study had dual primary endpoints of OS and rPFS and was powered to show superiority in rPFS and OS.

3.2. Favourable effects

A statistically significant treatment effect on OS in favour of apalutamide was observed. The HR for OS was 0.67 (95% CI: 0.51, 0.89; p=0.0053) meeting the pre-specific threshold of statistical significance at this interim analysis. At the time of data cut-off, median OS was not reached in either treatment group. The landmark OS rate at 24 months favored the apalutamide + ADT arm (82% of subjects compared with 74% of subjects in the placebo + ADT arm).

A statistically significant treatment effect on rPFS was observed in favour of apalutamide. The HR for rPFS was 0.48 (95% CI: 0.39, 0.60; p<0.0001). The alpha boundary of 0.005 was crossed. Median rPFS was not reached for the apalutamide + ADT arm and was 22 months for the placebo + ADT arm. The landmark event-free rate at 24 months favored the apalutamide + ADT arm (68% of subjects compared with 48% of subjects in the placebo + ADT arm).

As specified in the statistical plan, the rPFS endpoint was tested first at the two-sided 0.005 level of significance. Since rPFS was statistically significant, the OS endpoint was tested at the overall 0.05 level of significance. Median OS follow-up was approximately 22 months in both groups.

The statistical testing of the secondary endpoints had to be performed by using fixed sequence testing according to the following pre-specified order considering clinical importance and data maturity: time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to SRE.

Treatment with apalutamide + ADT significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.39, 95% CI: 0.27, 0.56; p < 0.0001). Median time to chemotherapy was not reached in either treatment group. Time to pain progression was then tested but did not cross the boundary. As a result, further secondary endpoints were not formally tested.

3.3. Uncertainties and limitations about favourable effects

While the statistical significance in OS was reached, the number of deaths was only approximately 50% of the number of events anticipated for conducting the final analysis of the trial. It is noted that the plan tried to detect an increase in the median OS from 44 in the control arm to 59 months in the apalutamide arm. However, due to the interim study termination there are a number of censored patients (852, 81%) with many of them in the first part of the curve. The study has also substantially less follow-up than planned. This is accepted considering the whole evidence in the target population and the lack of equipoise once there has been a substantial benefit in terms of rPFS. The MAH is also recommended to submit the updated OS results as soon as available.

The majority of the OS subgroups analysed support the ITT analysis. Only in the prior docetaxel group no favourable effect was detected with the point estimate above unity. However, due to the very low number of events, this result should be interpreted carefully.

3.4. Unfavourable effects

In TITAN, the most frequently reported TEAEs (≥15% of patients in either arm) was skin rash (grouped term), fatigue, back pain, hypertension, arthralgia, hot flush and weight increased. Apart from hot flush and weight increased, the other frequently reported TEAEs were also frequently reported TEAEs in SPARTAN. The majority of these events were Grade 1 or 2. With the exception of skin rash (grouped term), these events rarely led to treatment discontinuation (≤1.5%) or dose modification and were rarely considered to be SAEs (≤1.1%). Except for back pain, all of these frequently reported TEAEs are ADRs for apalutamide.

Grade 3-4 TEAEs were reported for 42% of patients in the apalutamide arm and 41% of patients in the placebo arm in TITAN (47% vs 35% in SPARTAN). Hypertension, skin rash (grouped term) and anaemia were the most frequently reported Grade 3 or 4 TEAEs.

TEAEs leading to death were reported for 1.9% of patients in the apalutamide arm and 3.0% of patients in the placebo arm in TITAN (1.6% vs 0.5% in SPARTAN).

Deaths were reported for 3.4% of patients in the apalutamide arm and 4.4% of patients in the placebo arm in TITAN.

Treatment was discontinued due to a TEAE in 8.0% of patients in the apalutamide arm and 5.3% of patients in the placebo arm in TITAN (11% vs 7.8% in SPARTAN). Skin rash (as a grouped term) was the most common TEAE leading to treatment discontinuation.

Dose was modified due to a TEAE in 23.0% of patients in the apalutamide arm and 13.0% of patients in the placebo arm in TITAN (33.0% vs 19.0% in SPARTAN). Skin Rash (grouped term) was the most common reason for dose reduction or interruption in the apalutamide + ADT arm in both studies.

Adverse events of special interest included as ADR for apalutamide are: skin rash, fall, fracture, seizure and hypothyroidism.

3.5. Uncertainties and limitations about unfavourable effects

The overall rate of cardiac disorders was slightly lower in TITAN *(8.8% apalutamide vs 5.9% placebo)* in comparison with SPARTAN (13% apalutamide vs 9.5% placebo). This may be related to differences in age (median age 68 years in TITAN vs 74 years in SPARTAN), weight (median weight 77 Kg in TITAN vs 84 kg in SPARTAN), exposure to ADT (71% received prior ADT for 3 months or less prior to randomization in TITAN) and history of cardiac risk factors (66% apalutamide and 61% placebo in TITAN; 75% vs 76% in SPARTAN) in the populations of both studies. However, although incidence of cardiac disorders is lower in TITAN, it is still higher for apalutamide arm, even in the group without history of cardiac risk factors prior to study entry.

Updated safety data is planned to be submitted together with the final OS analysis. There is currently insufficient evidence to propose an update of the product information in relation to arrhythmias, cardiac failure, deaths due to cardiac events, secondary primary cancer, cognitive deficit, cerebrovascular disorders, psychiatric disorders, hyperhidrosis, dry skin, alopecia, sinusitis, epistaxis and hyperkalaemia. The MAH should continue to closely monitor these events and report on these events when submitting the final CSR.

3.6. Effects Table

Table 62: Effects Table for Erleada in the treatment of mHSPC patients along with ADT (data cut-off: 23 November 2018; study is on-going)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
rPFS	time from randomization to first documentation of radiographic progressive disease or death due to any cause	HR 0.484 95%CI (0.391, 0.600) Landmark event-free rate at 24 months (68% vs 48%; apalutamide + ADT arm vs placebo + ADT arm respectively)			Median not reached in the apalutamide + ADT arm 22.08 months in placebo+ADT	TITAN study
OS	time from randomization to death from any cause	HR 0.671 95%CI (0.507, 0.890) Landmark OS rate at 24 months (82% vs 74%; apalutamide + ADT arm vs placebo + ADT arm respectively).			According to interim analysis plan the alpha boundary of 0.0101 was crossed Median survival times not reached in any arm OS data	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					insufficiently mature, with a high number and early distribution in time of the censored data	
Time to initiation of cytotoxic chemotherapy	Time from date of randomization to the date of initiation of cytotoxic chemotherapy	HR 0.391 95%CI (0.274, 0.558)			The following secondary endpoint, time to pain progression was not significant	
Unfavourable Effects (TEAEs)						
TEAEs	Overall incidence of AEs	N (%)	507 (96.8)	509 (96.6)		TITAN study
Grade 3-4	Incidence of AEs of grade 3 or 4	N (%)	221 (42.2)	215 (40.8)		
Leading Discontinuation	Incidence of discontinuations due to AEs	N (%)	42 (8.0)	28 (5.3)		
Deaths	Incidence of deaths	N (%)	18 (3.4)	23 (4.4)		
Deaths due to AEs	Incidence of deaths due to AEs	N (%)	10 (1.9)	16 (3.0)		
Skin Rash	All grade Grade 3-4	N (%)	142 (27.1) 33 (6.3)	45 (8.5) 3 (0.6)		
Fall	All grade Grade 3-4	N (%)	39 (7.4) 4 (0.8)	37 (7.0) 4 (0.8)		
Fracture	All grade Grade 3-4	N (%)	33 (6.3) 6 (1.3)	24 (4.6) 4 (0.8)		
Seizure	All grade Grade 3-4	N (%)	3 (0.6) 1 (0.2)	2 (0.4) 0		
Hypothyroidism	All grade Grade 3-4	N (%)	34 (6.5) 0	6 (1.1) 0		
Ischemic heart disease	All grade Grade 3-4	N (%)	23 (4.4) 10 (1.9)	8 (1.5) 1 (0.2)		

Abbreviations: AE (Adverse Event), AR (Adverse Reaction), ISS (Integrate Safety Summary), CSR (Clinical Study Report)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The combination of apalutamide and ADT has shown as most important effect a clinically meaningful delay in the progression of the disease. This benefit in postponing the progression of the tumour seems to translate in a longer survival. Results were consistent across the different subgroups of patients recruited into the clinical trial, regardless the volume or the risk of the disease.

The uncertainties related to the OS outcome are likely related to the immaturity of the data and updated OS data are expected to be provided by the MAH. A further important clinical effect was the delay of the initiation of cytotoxic chemotherapy, with the landmark at 24-month event-free rates favouring the apalutamide + ADT arm (91% vs 78%).

Safety results in TITAN study are overall in line with the known safety profile of apalutamide.

3.7.2. Balance of benefits and risks

Based on a randomised clinical trial, the use of apalutamide in combination with ADT has led to a substantial longer rPFS and OS. Even though there are uncertainties on the magnitude of the benefit in terms of OS, the results are considered important. Overall, the risks associated to this combination appear in principle manageable and in line with the already known safety profile of the drug, and, in view of the favourable effects, the benefit-risk balance is considered positive.

The combination increases the treatment options along with docetaxel and abiraterone, for patients with mHSPC, regardless the risk or volume of the disease.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Erleada for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) for Erleada based on the results of study 56021927PCR3002 (TITAN study), a randomised, double-blind, placebo-controlled phase 3 study comparing apalutamide plus ADT versus ADT in patients with mHSPC; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to reflect the new indication, to add a warning on ischaemic cardiovascular events and to reflect new safety and efficacy information. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to make editorial update to the SmPC and Labelling. The RMP version 2.3 is approved.